THE EXPERIENCE, CONTRIBUTORS, AND ETIOLOGY OF PAIN IN PEOPLE WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

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Abstract

Pain is a common symptom in patients with chronic obstructive pulmonary disease (COPD). This symptom can negatively affect physical activity levels, quality of life, and health outcomes. It has been shown that systemic inflammation, comorbidities, and symptoms (e.g., dyspnea or fatigue) may cause pain. Although previous research has determined the association between pain and the presence of comorbidities, the specific comorbidities that cause pain and other etiologic factors of pain are still unknown. Also, the interrelationships among pain, dyspnea, and fatigue and whether the presence of one symptom accentuates another remain to be examined.

The overall purpose of this dissertation was to investigate the etiology of pain by exploring the pain experience, the contributors to pain, the interrelationships between pain and other symptoms, and the associations between pain and thoracic abnormalities in patients with COPD. Studies I and II established the reliability and validity of the Brief Pain Inventory (BPI), Dyspnea Inventory (DI), and Brief Fatigue Inventory (BFI) in patients with COPD. Study III determined comorbidities that caused pain as well as compared pain, fatigue, and dyspnea symptomology in patients with COPD. This study utilized a cross-sectional survey design that included the BPI, DI, BFI, General Self-efficacy Scale, Clinical COPD Questionnaire, and Comorbidities/Medication Questionnaire. Study IV investigated chest computed tomography images of patients with COPD and current/ex-smokers to examine the associations between trunk pain and thoracic vertebral deformity and arthropathy.

The findings showed that the BPI, DI, and BFI were reliable and valid questionnaires to evaluate symptoms in COPD. Similar to dyspnea and fatigue, pain was also a significant symptom in patients with COPD and these three symptoms were correlated with each other. Further, the most common comorbidities that caused pain were musculoskeletal diseases. Trunk pain in patients with COPD was associated with thoracic vertebral deformities, arthropathy of thoracic joints, and hyperkyphosis.

In summary, pain in COPD is associated with musculoskeletal comorbidities and there are interactions between pain and other symptoms. This dissertation provides insight into the causes of pain in patients with COPD, which can facilitate the development of pain management strategies in COPD.

Lay Summary

Patients with chronic obstructive pulmonary disease (COPD), a smoking-related disease, frequently complain of pain. Pain interferes with being active among COPD patients, which can worsen their health and quality of life. This thesis investigated the causes of pain in COPD patients. We demonstrated that three questionnaires can consistently and accurately measure three common COPD symptoms: pain, tiredness, and breathlessness. Secondly, pain, tiredness, and breathlessness were found to be equally severe and affect 75% of COPD patients or more. Thirdly, musculoskeletal conditions were the most common cause of pain in COPD patients. Lastly, pain in the trunk appears to be due to arthritis and fractures related to brittle bones in the spine. In conclusion, COPD patients experience significant pain that can be severe and is only slightly less common than tiredness and breathlessness. Health care professionals need to address this symptom to enable physical activity and to improve quality of life.

Preface

The research studies in this dissertation were designed, conducted, analyzed, interpreted, and written by Yi-Wen Chen in consultation with Dr. W. Darlene Reid, the thesis supervisor, and Dr. Harvey O. Coxson, Dr. Michael A. Hunt, and Dr. Jordan A. Guenette, the supervisory committee members.

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List of Abbreviations

6MWT:	Six-minute walking test
BC-LHC:	British Columbia-Lung Health Cohort
BPI:	Brief Pain Inventory
BFI:	Brief Fatigue Inventory
BMI:	Body Mass Index
CAT:	COPD Assessment Test
CCQ:	Clinical COPD Questionnaire
CHAMPS:	Community Health Activities Model Program for Seniors
CI:	Confidence interval
CNS:	Central nervous system
COPD:	Chronic obstructive pulmonary disease
CRP:	C-reactive protein
CRQ:	Chronic Respiratory Questionnaire
CRQ-SAI:	Self-administrated CRQ with an individualized dyspnea domain
CRQ-SAS:	CRQ with a standardized dyspnea domain
CT:	Computed tomography
CVD:	Cardiovascular diseases
DI:	Dyspnea Inventory
DXA:	Dual-energy X-ray absorptiometry
FEV_1:	Forced expiratory volume in one second
fMRI:	Functional magnetic resonance imaging

FVC:	Forced vital capacity
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GSE:	General Self-efficacy Scale
HU:	Hounsfield unit
ICC:	Intraclass correlation coefficients
IL-1:	Interleukin-1
IL-1β:	Interleukin-1beta
IL-6:	Interleukin-6
IL-8:	Interleukin-8
LLN:	Lower limit of normal
MCS:	Mental Component Summary
MPQ:	McGill Pain Questionnaire
mMRC:	Modified British Medical Research Council
OR:	Odds ratio
PCS:	Physical Component Summary
PET:	Positron emission tomography
SDI:	Spinal Deformity Index
SF-36:	Medical Outcomes Study Short Form-36
TNF-α:	Tumor necrosis factor alpha

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To my beloved family

Chapter 1: Introduction

1.1 Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a common and debilitating respiratory condition that involves progressive and irreversible airflow limitation. While the etiology of COPD is not well understood, it is generally well accepted that chronic inflammatory responses within the lung parenchyma and airways are the primary cause of both the lung destruction and airway remodeling present in this disease.[1] The primary diagnosis of COPD is based on spirometry, with two competing definitions of airflow obstruction. The first diagnostic definition is based on a fixed ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) being less than 0.7.[1] In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were published for classifying COPD severity.[2] Using the GOLD criteria, patients with COPD are divided into levels of severity based on the extent of airflow obstruction (FEV_1 as a percent of predicted) as indicated in Table 1.1.[2] The GOLD guidelines for COPD classification were updated in 2011 to also include symptoms and exacerbation history (Table 1.2).[3] The second definition of COPD diagnosis is the FEV_1 and FVC ratio being below the lower limit of normal (LLN).[4] While these two definitions of COPD differ in their interpretation of spirometric results, both criteria stress the debilitating loss of lung function that ultimately results in decreased quality of life and, in many cases, death.

Table 1.1 GOLD criteria based on airflow limitation

	FEV_1/ FVC	FEV_1 (% predicted)
GOLD I: Mild	< 0.7	≥ 80
GOLD II: Moderate	< 0.7	50 – 79
GOLD III: Severe	< 0.7	30 – 49
GOLD IV: Very severe	< 0.7	< 30

Abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease

Table 1.2 Refined GOLD criteria that include assessments of symptoms and exacerbations

GOLD grade	GOLD classification of airflow limitation	Exacerbation per year	Symptom	
			mMRC	CAT
A: Low risk, less symptoms	GOLD I – II	0 – 1	0 – 1	< 10
B: Low risk, more symptoms	GOLD I – II	0 – 1	≥ 2	≥ 10
C: High risk, less symptoms	GOLD III – IV	≥ 2	0 – 1	< 10
D: High risk, more symptoms	GOLD III – IV	≥ 2	≥ 2	≥ 10

Abbreviations: CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified British Medical Research Council questionnaire

1.1.1 Prevalence of COPD

The reported prevalence of COPD differs among the current studies because of the different diagnostic criteria and definitions of COPD used. It has been shown that the prevalence of COPD that is derived from a self-report is lower than that diagnosed by spirometry.[5] Also, the use of pre- or post-bronchodilator spirometry with different diagnostic criteria, i.e. fixed ratio or LLN, can produce variable prevalence estimates of COPD.[6] A systematic review conducted by Adeloye et al.[7] in 2010 included 123 studies and reported that the estimated number of COPD cases was 384 million among individuals aged 30 years and older, resulting in a worldwide prevalence of 11.7%. In Canada, the estimated prevalence of COPD is 16.6% among 2.6 million Canadians aged 35 to 79 years.[5] While the results from the COPD prevalence studies can vary, there is no doubt that COPD is a devastating disease with major health and economic consequences.[8]

1.1.2 Causes and risk factors that can contribute to COPD

Cigarette smoking has been recognized as a primary risk factor for COPD.[9] Studies have shown that smoking can lead to airway inflammation[10] and parenchymal destruction of the lungs.[9] These inflammatory related changes are permanent and the inflammation does not stop even after smoking cessation.[11] However, not all smokers develop abnormal lung function and/or COPD.[12] This has led investigators to examine other causes of COPD such as genetic factors,[13] air pollution, occupational exposures to hazardous substances, infections,[1 14] and abnormal lung development.[15] A well-described genetic cause of COPD is α_1- antitrypsin deficiency where the serum protective protein, α_1- antitrypsin, is not manufactured in sufficient quantity to protect the lung from the side effects of a chronic inflammatory response.[16] While this is the most well

understood genetic cause of COPD, there are numerous studies that have found other genes associated with the development of COPD.[17] In addition, although cigarette smoking is the most common risk factor for COPD in the developed world, exposure to airborne particles, indoor biomass fuel smoke, and general air pollution can cause COPD, especially in developing countries.[18-20] Therefore, the risk factors for COPD are numerous, which gives rise to the development of the symptoms seen in COPD.

1.1.3 Symptoms of COPD

Patients with COPD frequently experience multiple symptoms in addition to airflow limitation including dyspnea, cough, sputum production, fatigue, pain, and sleeplessness.[3 21 22] In a study that investigated multiple symptoms in 100 patients with COPD, Bentsen et al.[21] found that 88% of participants reported having more than one symptom. An observational study by Miravitlles et al.[23] also reported that among 727 patients with stable COPD, 82.7% had more than one symptom. Importantly, the number of symptoms that a patient has can be quite extensive. For example, Edmonds et al.[24] reported that patients with COPD experienced 7.1 ± 2.9 different symptoms in the final year of their life.

Several studies have investigated multiple symptoms in patients with COPD. Table 1.3 summarizes the prevalence of multiple symptoms in the current literature. Dyspnea is the most common symptom in patients with COPD, followed by fatigue. Studies have shown that the prevalence of dyspnea ranged from 94% to 100%.[21 24-29] Compared to dyspnea, the prevalence of fatigue in patients with COPD is somewhat lower but still considerable with 55% to 96% of patients with COPD reporting fatigue.[21 25-29] It is also noteworthy that cough, pain, and sleeplessness are commonly reported in patients with COPD with the prevalence ranging from

56% to 80%, 32% to 77%, and 28% to 77%, respectively.[21 24-29] Other COPD symptoms are thirst, loss of appetite, low mood, wheezing, and sputum production.[3 24-29] A smaller proportion of patients with COPD also experience dizziness, nausea, constipation, diarrhea, and vomiting.[24 27 29]

In summary, patients with COPD suffer from a variety of symptoms. Among these symptoms, dyspnea, fatigue, pain, cough, and sleeplessness are the most prevalent. Importantly, patients with COPD may experience many of these symptoms simultaneously, which leads to a reduction in their quality of life.[27]

Table 1.3 The prevalence of multiple symptoms in patients with COPD

Author (year)	Sample	Prevalence						
		Dyspnea	Fatigue	Pain	Cough	Sleeplessness	Thirst	Other symptoms
Skilbeck (1998)[25]	63 patients with end stage COPD	95%	68%	68%	--	55%	54%	
Edmonds (2001)[24]	87 dying COPD patients	94%	--	77%	59%	65%	--	No appetite: 67% Low mood: 71%
Elkington (2005)[26]	209 dying COPD patients	98%	96%	72%	80%	77%	--	No appetite: 81% Low mood: 77%
Blinderman (2009)[27]	100 patients with severe to very severe COPD	94%	71%	37%*	56%	35%	60%	Wheezing: 40%
Janssen (2011)[28]	105 patients with severe to very severe COPD	94%	89%	32%	58%	51%	38%	No appetite: 35% Low mood: 52%
Bentsen (2013)[21]	100 patients with moderate to very severe COPD	100%	72%	45%	--	28%	--	
Eckerblad (2014)[29]	91 patients with moderate or severe COPD	90%	55%	44%	65%	52%	65%	Dizziness: 28%

*Chest pain

1.1.4 Management of COPD

At present, there is no cure for COPD. Based on the most up-to-date GOLD clinical practice guidelines published in 2017,[1] the management of stable COPD includes pharmacologic and non-pharmacologic treatments. The most common medications used in patients with COPD are bronchodilators and glucocorticoids.[30] Since there is no known cure for COPD, the aims of pharmacologic treatments are to alleviate symptoms, decrease the future risk of exacerbations, and improve exercise capacity and health status.[1] Similarly, non-pharmacologic treatments such as regular physical activity, smoking cessation, oxygen therapy, ventilatory support, and surgery[1 3 31] are all designed to reduce symptoms and improve quality of life.

With respect to non-pharmacologic therapies, pulmonary rehabilitation is a well-established standard of care and has been recommended for patients with symptomatic COPD.[30] Pulmonary rehabilitation is a comprehensive program that includes assessments, exercise, education, nutrition consultation, and psychosocial support.[32] It has been shown that the BODE composite index (Body mass index (BMI), airflow Obstruction, Dyspnea, and Exercise capacity) is associated with mortality in patients with COPD.[33] Importantly, pulmonary rehabilitation can improve the BODE index, which is beneficial to the clinical and health status outcomes in COPD.[34]

One key feature of pulmonary rehabilitation is the maintenance of physical activity and exercise engagement in patients with COPD. The current literature has shown the benefits of increasing physical activity levels in patients with COPD. In a systematic review that included five studies, Chavannes et al.[35] concluded that engaging in physical activity could improve fitness levels in patients with COPD. In addition, Garcia-Aymerich et al.[36] conducted a

population-based cohort study that included 2,386 patients with COPD and found that compared with patients with COPD who had very low physical activity levels, the risk of hospital admission and mortality was lower in those who reported low, moderate or high physical activity. In 2014, Gimeno-Santos et al.[37] published a systematic review and also summarized that the level of physical activity in COPD was associated with mortality and COPD exacerbations. As a result, the American Thoracic Society,[38] European Respiratory Society,[38 39] GOLD,[3] and Canadian Thoracic Society[40] all have advocated the benefits of regular physical activity and recommended it for patients with COPD. Increasing physical activity levels and improving long-term adherence to physical activity are two of the goals of pulmonary rehabilitation for patients with COPD.[41]

Although the current evidence has shown the benefits and importance of keeping a physically active lifestyle, patients with COPD have significantly lower physical activity levels and limited adherence to physical activity compared with those without COPD. In a systematic review published in 2011, Bossenbroek et al.[42] found that the daily physical activity levels and intensities of patients with COPD were significantly lower than healthy individuals. Another literature review conducted by Vorrink et al.[43] in 2011 also summarized that patients with COPD had significantly reduced physical activity levels than an age-matched healthy cohort. Therefore, identifying the barriers to remaining physically active in patients with COPD is important in order to improve the engagement in physical activity.

In a recent qualitative study, Kosteli et al.[44] recruited and interviewed 26 patients with COPD from a primary care setting and found that the barriers to physical activity participation were health-related, psychological, attitudinal, and motivational factors. Of those, physical

limitations due to symptoms of COPD were the primary impediment for patients with COPD to perform physical activity. For example, dyspnea and fatigue, two major symptoms of COPD, could contribute to physical inactivity and exercise intolerance. Katajisto et al.[45] reported that the perception of dyspnea was strongly correlated with exercise activity, daily life activity, and mobility levels in patients with COPD. Similarly, Woo[46] found that physical activity, dyspnea, and fatigue were significantly interrelated after adjusting for age and FEV_1. Breslin et al.[47] also claimed that general fatigue was correlated with exercise intolerance. Dyspnea and fatigue have also been shown to be the major reasons that patients with COPD are not able to continue performing physical activity or exercise. In a clinical study, Killian et al.[48] performed symptom-limited incremental cycle exercise tests in 105 patients with clinically stable COPD. They found that 61% and 18% of participants specified dyspnea and leg fatigue, respectively, as the primary reason for stopping the exercise tests.

In addition to dyspnea and fatigue, pain appears to be an important obstacle to participation in physical activities in patients with COPD.[49 50] The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damages".[51] In the most recent qualitative study, Harrison et al.[52] interviewed 18 health care providers and 19 patients with COPD who attend pulmonary rehabilitation programs to explore pain experience and the impact of pain on participation in the programs. The authors concluded that pain could impede patients with COPD from fully participating in pulmonary rehabilitation programs. They also found that health care providers rarely ask about pain and patients with COPD usually do not report pain to health care providers. Therefore, in comparison with dyspnea and fatigue, pain is

an under-appreciated and under-investigated symptom in patients with COPD. Nonetheless, pain has recently gained more attention from researchers, as its role in limiting physical activity is becoming more fully understood. The following sections discuss the research literature on pain in patients with COPD.

1.2 Pain in patients with COPD

1.2.1 Prevalence of pain

The reported prevalence of pain in patients with COPD varies greatly in the current literature. A systematic review conducted by van Dam van Isselt et al.[53] in 2014 reported that the prevalence of pain in the 11 included studies ranged from 21% to 72.1%. In another systematic review published in 2015,[54] Lee et al. performed a meta-analysis to combine six studies and concluded that the pooled prevalence of pain in patients with moderate to very severe COPD was 66%. The variability in the reported prevalence of pain may derive from the heterogeneity of participants' demographics in the studies. Although patients' descriptions and self-report provide the most reliable and accurate evidence for the presence of pain,[55] the perception of pain may be influenced by culture,[56 57] race,[58 59] age,[60] and sex.[57]

Early studies that were published before 2011 predominantly investigated various symptoms in patients with end-stage COPD[24-26 61] or those with severe COPD[27 62] in order to determine the needs of palliative care patients. Pain was merely one of the examined symptoms in these early studies. The prevalence of pain in patients with COPD who require palliative care ranged from 32.4% to 77%.[24-27 61 62] However recently, clinicians and investigators have recognized the significance of pain in patients with COPD and started to focus on investigating

pain in those with clinically stable COPD or pulmonary rehabilitation program attendants with any stage of COPD. The prevalence of pain in these studies was reported to range between 32.4% and 82.1%.[28 29 49 63-69] Moreover, the prevalence of pain was significantly higher in patients with COPD than that in the general population[63 69] and individuals with other chronic diseases.[70] These results correspond with the study published by HajGhanbari et al.[49] in 2012. They found that the number of COPD patients with pain was 2.2 and 7.5 times higher than an age- and sex-matched health cohort using the Brief Pain Inventory (BPI) and McGill Pain Questionnaire (MPQ), respectively.

In summary, the current literature showed that at least one-third of patients with COPD experienced pain and the prevalence of pain was significantly higher in patients with COPD when compared with the general population. Table 1.4 summarizes the results of the current studies that investigated the prevalence of pain in patients with COPD.

Table 1.4 Studies that investigated the prevalence of pain in patients with COPD

Author (year)	Sample size (M/F)	Age (years)	COPD severity	FEV_1 (% predicted)*	Instrument	Results/ Prevalence of pain
Palliative care patients						
Lynn (1997)[61]	222		End-stage		Post-bereavement structured interviews	34%
Skilbeck (1998)[25]	63 (33/30)	71	End-stage		In-depth interview	68%
Edmonds (2001)[24]	87 (65/22)		End-stage		Post-bereavement structured interviews	Pain in the final year of life: 77%
Elkington (2005)[26]	209 (115/94)		End-stage		Post-bereavement surveys	72%
Blinderman (2009)[27]	100 (47/53)	62.2 (10.5)	Severe to very severe	24.4 (3.9)	Memorial Symptom Assessment Scale	Non-chest pain: 41% Chest pain 37%
Lohne (2010)[62]	16 (3/13)	57.8 (4.1)	Severe to very severe	21.1 (5.8)	Semi-structured interview	Patients with COPD reported an average pain score of >6: 38%
Pulmonary rehabilitation program/ outpatient participants/ clinically stable patients						
Janssen (2011)[28]	105 (65/40)	66.3 (9.2)	Severe to very severe	34.1 (13.5)	Visual analogue scale	Moderate to severe pain: 32.4%
Bentsen (2011)[63] (2014)[64]	COPD: 100 (51/49) General population: 993	COPD: 66.1 (18.3)	Moderate to very severe	46 (15)	0-10 numeric rating scale	The prevalence of pain was significantly higher in patients with COPD (45%) than that in the general population (34%).
Borge (2011)[65]	154 (79/75)	64.6 (10.2)	Mild to very severe		BPI	72.1%
HajGhanbari (2012)[49]	COPD: 47 (27/20) Healthy: 47 (27/20)	COPD: 70 (6.7) Healthy: 68.2 (8.8)	Moderate to severe	44.7 (19.2)	BPI, MPQ	The number of COPD patients with pain was 2.2 and 7.5 times higher than healthy people evaluated by

Author (year)	Sample size (M/F)	Age (years)	COPD severity	FEV_1 (% predicted)*	Instrument	Results/ Prevalence of pain
						the BPI and MPQ, respectively.
Eckerblad (2014)[29]	91 (43/48)	67	Moderate and severe	Moderate: 61.6 (8.4) Severe: 42.2 (5.8)	Memorial Symptom Assessment Scale	44%
HajGhanbari (2014)[66]	54	72	Moderate to severe	48.3	BPI, MPQ	81%
Christensen (2016)[67]	258 (121/137)	63	Moderate to severe	38.5	BPI	61%
Janssen (2016)[68]	67 (40/27)	64.9 (10.2)	Mild to very severe	50 (20.3)	Multidimensional, structured pain interview	82.1%
Lee (2017)[69]	COPD: 64 (30/34) Healthy: 64 (30/34)	COPD: 71 (10) Healthy: 67 (13)	Moderate to very severe	37.9 (14.9)	BPI, EABPS, S-LANSS, Pain Catastrophizing Scale	The prevalence of pain was significantly higher in patients with COPD (41%) than the control group (29%).
Population-based survey						
Roberts (2013)[70]	COPD: 7952 (3340/4612) Non-COPD: 15904 (6680/9224)	COPD: 69.3 Non-COPD: 68.4			ICD-9-CM diagnosis code, claims for pain therapy or pain medication	The prevalence of pain was significantly higher in patients with COPD (59.8%) than non-COPD patients (51.7%).

*Data of FEV_1 values only presented in COPD patients. Age and FEV_1 are presented as mean (SD)

Abbreviations: BPI = Brief Pain Inventory; EABPS = Extended Aberdeen Back Pain Scale; ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification; MPQ = McGill Pain Questionnaire; S-LANSS = Self-reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale

1.2.2 Characteristics of pain

Patients with COPD frequently identify pain in the trunk region,[53 54] which includes the neck, shoulder, chest and back areas. A recent cross-sectional study conducted by Janssen et al.[68] showed that more than half of the participants (53.7%) had chest pain. Bentsen et al.[63] and Lee et al.[69] also reported that the majority of patients with COPD identified pain in the chest area. Likewise, Blinderman et al.[27] and Lohne et al.[62] examined pain in patients with advanced COPD and found 37% and 38% of patients had chest pain, respectively. Other commonly reported pain locations among patients with COPD include the shoulder, neck, and low back. In a qualitative study included 16 patients with severe COPD, Lohne et al.[62] found that half of the patients reported pain in the shoulder, neck, and upper arm areas. Borge et al.[65] found that 33.1% of patients with COPD self-reported that the most common pain location to be the shoulder followed by lower back, which was reported by 29.2% of patients with COPD. In the study by Christensen et al.,[67] 47.4% of patients with COPD had low back pain followed by shoulder pain (46.2%). Two studies conducted by HajGhanbari et al. in 2012[49] and 2014[66] found that the neck was the most common location of pain in patients with COPD. Taken together, although the most common pain location is slightly different among studies, it is noteworthy that the trunk is where patients with COPD complain the most about their pain.

Mild to severe pain intensity and interference have been found in patients with COPD in several studies. The mean scores of pain intensity and interference measured by the BPI were reported by four studies[49 65-67] ranging from 2.8 to 3.9 and 3.1 to 4.4 out of 10, respectively, which indicated mild to moderate pain intensity and interference.[71] However, Bentsen et al.[63 64] used 0 to 10 numeric rating scales to quantify pain intensity and interference in patients with

COPD and discovered that the levels of pain intensity and interference ranged from moderate to severe. They also reported that the worst pain intensity level in patients with COPD was severe.[63]

Comparisons of pain intensity and interference levels between patients with COPD and the general population remain inconclusive. HajGhanbari et al.[49] compared pain intensity and interference, measured by the BPI and MPQ, between 47 patients with COPD and 47 age- and sex-matched healthy individuals. The authors reported that the pain intensity and interference scores were significantly higher in patients with COPD. Also, patients with COPD reported 2.5 and 3.7 times higher pain intensity and interference with aspects of daily living than the healthy cohort. Similarly, Lee et al.[69] studied pain in 64 patients with COPD and 64 age- and sex-matched healthy individuals and found that patients with COPD had greater pain intensity measured using the BPI than the control group (3.8 vs. 2.7 out of 10). In contrast, Bentsen et al.[63] found that there was no significant difference in the pain intensity and interference scores between patients with COPD and the general population after adjusting for age and sex. This apparent inconsistency may be ascribed to the demographic characteristics of patients with COPD and the controls. Also, pain-related comorbidities were similarly distributed in patients with COPD and the general population in the study by Bentsen et al.,[63] whereas HajGhanbari et al.[49] found that patients with COPD had a higher number of comorbidities than age- and sex-matched healthy individuals. Therefore, the difference in the distribution of comorbidities and participant demographics between these two studies might, in part, explain the inconsistent results.

1.2.3 Impact of pain

The presence of pain can adversely affect the physical status of patients with COPD. Pain has been shown to be negatively associated with physical activity levels in patients with COPD. In a cross-sectional study that included 26 patients with moderate to severe COPD, HajGhanbari et al.[50] found that the pain intensity scores measured by the BPI and MPQ were negatively correlated with the results of six-minute walk test (6MWT). Also, participants with severe pain had a lower physical activity level and worse functional exercise capacity measured by the 6MWT than those with minimal or no pain. Similar results have been demonstrated in another study by HajGhanbari et al.,[49] in which the authors concluded that among patients with COPD, the higher pain interference scores were correlated with greater pain-related fear of movement or re-injury and lower total energy expenditure measured by the modified Tampa Scale for Kinesiophobia and the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire, respectively. Moreover, a study by Lee et al.[69] showed that COPD patients with pain had lower physical activity levels that were assessed using the StepWatch Activity Monitor. Compared to COPD patients without pain, the step count and proportion of time spent performing medium or high intensity activity were significantly lower in those who experienced pain.

In addition, pain can negatively impact quality of life in patients with COPD. Borge et al.[65] revealed that the BPI pain intensity and interference scores were negatively associated with disease-specific quality of life measured by the Respiratory Quality of Life Questionnaire in patients with COPD. HajGhanbari et al.[50] also concluded that the increased pain intensity scores were correlated with worse health-related quality of life assessed by the Medical Outcomes

Study Short Form-36 (SF-36). These results were also found in the study conducted by Bentsen et al.,[64] in which they reported that COPD patients with pain had worse disease-specific and generic quality of life assessed by the St. George's Respiratory Questionnaire and Quality of Life Scale, respectively. Similarly, based on the findings of the study by Janssen et al.,[68] pain in patients with COPD was associated with worse disease-specific health status that was measured by the CAT.

Pain can also impose a heavy economic burden on the medical system. In 2015, Roberts et al.[72] conducted a retrospective population-based study that included 7,952 patients with COPD and reported that those with pain had a significantly higher annual direct medical cost than those without pain ($24,261 versus $10,390).

In summary, pain reduces the physical activity levels, exercise capacity, and quality of life as well as increases medical expenditure in patients with COPD.

1.3 Possible factors that can cause and/or contribute to pain

The etiology of pain in patients with COPD remains to be determined. The factors that may cause pain are described in the following sections.

1.3.1 Systemic inflammation

It is well documented that COPD is a systemic disease that involves a series of local and peripheral inflammatory responses.[73] Inhaled toxic chemicals or particles activate the innate immune system and affect the function of immune cells, such as macrophages, neutrophils, lymphocytes, and epithelial cells,[74] [75] which can lead to the release of pro-inflammatory

cytokines.[76] Several pro-inflammatory cytokines such as C-reactive protein (CRP), fibrinogen, leukocytes, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8)[77] [78] have been found to be high in the systemic circulation of patients with COPD. Other pro-inflammatory cytokines, including interleukin-1 (IL-1),[75 76] interleukin-1 beta (IL-1β),[75 79] TNF-α receptors,[76 80] and granulocyte macrophage-colony-stimulating factor[75 76] have also been found to be associated with systemic inflammation of COPD. All of these findings have led investigators to conclude that "COPD begins as a local inflammation in the lungs and this leads – through differentiated pathways yet to be fully clarified – to systemic consequences".[81]

Coincidentally, several pro-inflammatory cytokines that cause systemic inflammation are associated with the occurrence and persistence of pain, such as CRP, TNF-α, IL-6, and IL-8.[82] Pain is an alerting sensation and is one of the typical signs of inflammation.[83] When tissues are injured or stimulated, certain pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-α, are produced by immune cells and move to the damaged sites.[83 84] The release of these pro-inflammatory cytokines can activate pain nociceptors,[85] i.e. A-δ and C fibers, that are responsible for transmitting pain signals to the central nervous system (CNS).[86]

Moreover, these pro-inflammatory cytokines can induce hyperalgesia and reduce pain thresholds.[87-89] Previous studies have found that IL-1β, TNF-α, IL-6, and IL-8 could induce hyperalgesia in rats.[90-92] In addition to animal studies, clinical human studies have also shown the relationship between pro-inflammatory cytokines and pain thresholds. It has been reported that the higher levels of CRP and IL-6 are related to lower pain thresholds and tolerance.[88 93]

To conclude, systemic inflammation can facilitate the production of certain pain-related pro-inflammatory cytokines and could change pain thresholds in patients with COPD. To date,

only one study that had a small sample size (n=19) reported that patients with COPD had lower pain thresholds compared to controls.[94] Therefore, future research regarding the association between changes in pain thresholds and the levels of pro-inflammatory cytokines in patients with COPD is required in order to determine the role of systemic inflammation in pain.

1.3.2 Comorbidities

It is well known that COPD involves both pulmonary and extra-pulmonary effects and, therefore, is associated with the presence of comorbidities.[95 96] Patients with COPD frequently suffer from several comorbidities, which are associated with adverse health outcomes, such as increase in mortality,[97 98] exacerbations,[99] and hospitalizations,[100] as well as poor quality of life.[101] Dal Negro et al.[102] investigated comorbidities in 1,216 patients with COPD and found that 78.6% of them had at least one comorbidity; 68.8% had at least two comorbidities; and 47.9% had three or more comorbidities. They also reported that the mean number of comorbidities was 2.6 per patient. Similarly, in a longitudinal study that included 5,924 patients with COPD, Worth et al.[103] reported that 78.3% of patients with COPD suffered from at least one comorbidity. Therefore, the presence of comorbidities is very common among patients with COPD and the majority of these patients can have multiple comorbidities. According to the current literature, the most common types of comorbidities in COPD are cardiovascular diseases (CVDs), followed by musculoskeletal diseases.[66 102 104 105]

The presence of comorbidities in COPD is also associated with pain. HajGhanbari et al.[50] concluded that COPD patients with severe pain had 2 to 3 more comorbidities on average than those with minimal or no pain. Moreover, the authors found that the number of comorbidities was positively correlated with pain severity and interference scores measured by the BPI. In a

cross-sectional study, Bentsen et al.[105] reported similar results that patients with COPD who reported pain had a higher number of comorbidities compared with those without pain. In another study by HajGhanbari et al.,[66] among patients with COPD who had pain, 89%, 66%, and 30% of them self-reported more than one, one to four, and five to eight comorbidities, respectively. Although the association between pain and the presence of comorbidities has been determined in patients with COPD, the specific comorbidities that cause pain in patients with COPD remain to be identified. The following sections discuss the comorbidities that may cause pain in COPD.

1.3.2.1 Musculoskeletal diseases

Musculoskeletal diseases are among the primary causes of pain. In a telephone survey study, Blyth et al.[106] found that the prevalence of chronic pain was 22.1% and musculoskeletal diseases were the most common cause, which accounted for 26% of chronic pain. Likewise, Toblin et al.[107] studied chronic pain in the general population and concluded that 26% of participants reported pain, and that arthritis (31.3%) was the most common cause of pain. Also, Cimmino et al.[108] reported that approximately 30% of the general population had pain caused by musculoskeletal diseases.

Similarly, musculoskeletal diseases can lead to pain in patients with COPD. In the study by Bentsen et al.,[105] the prevalence of musculoskeletal diseases was higher in COPD patients with pain when compared with COPD patients without pain. Osteoporosis[109 110] and osteoarthritis[50 104] are two common age-related musculoskeletal diseases in COPD and may cause pain. The following sub-sections describe each musculoskeletal disease and how they may contribute to pain in patients with COPD.

1.3.2.1.1 Osteoporosis and osteoporotic fractures

Approximately one-third of patients with COPD are affected by osteoporosis. In a systematic review published in 2009, Graat-Verboom et al.[110] included 13 studies and concluded that the mean prevalence of osteoporosis was 35.1% in patients with COPD. Also, in the most up-to-date systematic review and meta-analysis (unpublished) in 2017,[111] the authors included 55 studies and reported that the global pooled prevalence of osteoporosis was 36% (95% CI = 31 − 40) in patients with COPD.

In spite of the high prevalence in COPD, the progression of osteoporosis is usually asymptomatic,[112] until its sequela, osteoporotic fractures, occurs. Vertebrae are the most common location of osteoporosis,[113] which can lead to vertebral deformities (i.e. vertebral compression fractures) and significantly increase in pain.[114] It has also been reported that the prevalence of vertebral deformities in patients with COPD ranged from 31% to 63.3%,[115 116] which was significantly greater than controls.[115] Moreover, vertebral deformities can change spinal morphology and increase thoracic kyphosis angles.[117-119] An increased thoracic kyphosis angle may also alter adjacent musculoskeletal alignment[119] and impose excessive stress on musculoskeletal structures,[120 121] which can induce pain. Taken together, osteoporosis can progress to osteoporotic fractures and further increase thoracic kyphosis angles, which may cause pain in patients with COPD.

1.3.2.1.2 Osteoarthritis and arthropathy

Osteoarthritis is another common age-related chronic condition that affects 40% of the elderly population in Canada who are over 70 years of age.[122] Osteoarthritis frequently occurs in the hip, knee, shoulder, hand, foot, and vertebral joints with pain and limited range of motion

being the common symptoms.[123] The current literature has revealed that the prevalence of osteoarthritis in patients with COPD ranged from 12.5% to 42%.[50 124 125] It is well known that joint misalignment, muscle weakness, and structural fragility of the joints are among the risk factors for osteoarthritis.[126]

In patients with COPD, excessive gas trapping in the lungs can cause a hyper-expanded chest wall, which may change the morphology of the chest wall and cause misalignment of the rib cage.[127 128] Also, lung hyperinflation leads to decreased chest wall compliance and shortens inspiratory muscles,[129] which in turn increases the workload of breathing and demands on the respiratory muscles.[130] This may contribute to a muscle imbalance, altered anatomical configuration of respiratory muscles, and predispose to chest wall muscle fatigue in some patients with COPD.[131 132] As a result, lung hyperinflation and changes in chest wall structures might be the risk factors for developing arthropathy (an umbrella term for degenerative joint disease)[133] in the joints between the ribs and spine. This arthropathy can be a potential cause of pain in patients with COPD.

1.3.2.2 Cardiovascular diseases

The World Health Organization defines CVDs as a group of disorders of the heart and blood vessels.[134] Chest pain or angina is a primary symptom in individuals with hypertension,[135] coronary artery disease,[136 137] heart failure,[138 139] and myocardial infarction.[140] In a systematic review, Solano et al.[141] found that 41% to 77% of patients with heart disease complained of pain. In addition, individuals with peripheral artery disease may experience calf or leg pain that is linked to intermittent claudication.[142]

Angina and chest pain are also reported in patients with COPD. Bentsen et al.[105] found that in 45 COPD patients with pain, 20% had angina, while Yeo et al.[104] reported a higher prevalence (37%) of angina in patients with COPD. Also, chest pain is reported in several studies with the reported prevalence ranging from 37% to 53.7% in patients with COPD.[27 62 68] However, these studies did not examine the causality of chest pain and CVD-related comorbidities and, therefore, it is unclear whether angina/chest pain in these COPD patients was caused by CVDs.

1.3.2.3 Other comorbidities that may cause pain

Other comorbidities that may cause pain include diabetes, anxiety, depression, and cancer. The following paragraphs discuss each comorbidity and its association with pain.

Diabetes occurs in 10% to 21% of patients with COPD[143-146] and it is associated with neuropathic[147] and calf pain due to intermittent claudication.[148] A cross-sectional study conducted by Davies et al.[149] reported that the prevalence of diabetic neuropathic pain was 26.4% in patients with diabetes. Also, it has been shown that diabetes is one of the risk factors for peripheral artery disease and, therefore, can contribute to intermittent claudication.[150] In a population-based survey study that involved 19,712 participants, Jensen et al.[151] reported that the prevalence of diabetes was 2.4%. Among those with diabetes, 3.5% had intermittent claudication, which is associated with pain.

Depression and anxiety, two psychological comorbidities, have been reported in approximately one-third of patients with COPD. In a recent systematic review published in 2016, Matte et al.[152] found that the pooled prevalence of depression in patients with COPD was 27.1%, which was significantly higher than the controls (10%). On the other hand, Willgoss et al.[153] reported in their systematic review that the prevalence of anxiety among patients with COPD

ranged from 6% to 33%. It has been documented that depression or anxiety could lower pain thresholds and enhance pain sensitivity.[154 155] Although depression and anxiety do not directly cause pain, these two psychological comorbidities can negatively change pain perception. The results of two COPD studies confirm the statements above. Borge et al.[22] investigated several symptoms in patients with COPD and reported that pain intensity measured by the BPI was positively correlated with depression and anxiety assessed using the Hospital Anxiety and Depression Scale. Similarly, Roberts et al.[70] reported that the risk of having chronic pain in COPD patients with depression was 2.22 times higher than those without depression. However, the association between pain and anxiety was not examined in their study.

Cancer is one of the comorbidities experienced by people living with COPD. Studies have revealed that the prevalence of cancer in patients with COPD is between 6% and 9%.[66 97 105] Although the prevalence of cancer is lower than other comorbidities, cancer has been reported to be the major cause of death in patients with COPD.[98] Importantly, the most significant symptom of cancer is pain. In a systematic review, van den Beuken-van Everdingen et al.[156] found that over 50% of patients experienced pain in all cancer types. More specifically, lung cancer and COPD are interrelated and share the same risk factors.[157 158] Despite a lack of reported prevalence of lung cancer in patients with COPD, it is expected that lung cancer is a common cancer type in this patients population.[159 160] In addition, it has been shown that the prevalence of pain in patients with lung cancer is 55%.[156]

In summary, several comorbidities may coexist with COPD and a primary symptom of these numerous comorbidities is pain. Research regarding whether pain is caused by certain comorbidities in patients with COPD is required.

1.3.3 Associations between symptoms

In 1995, Lenz et al.[161] first proposed the theory of unpleasant symptoms and updated it in 1997.[162] This theory highlights that multiple unpleasant symptoms, such as pain, dyspnea, fatigue, and nausea, can be triggered by similar physiological, psychological, as well as situational factors and occur simultaneously. Also, multiple symptoms can interact synergistically such that a symptom can appear to be worse when it occurs in concert with others compared to if it occurs alone.

Among the multiple symptoms of COPD, the association between dyspnea and pain has been determined. The commonalities of dyspnea and pain perception have been recognized and several similar physiological and psychological features can be found in both symptoms. First, dyspnea and pain are alerting sensations, which are caused by a noxious stimulus or a disturbed physiological state.[163] Therefore, both symptoms are involved with the detection of stimulants, activation of nociceptors and afferent nerves, as well as the transmission of signals to the CNS.[86] [164] Second, numerous brain imaging studies have shown that the perception of dyspnea and pain can activate similar cortical responses. For example, studies using positron emission tomography (PET)[165 166] or functional magnetic resonance imaging (fMRI)[167] demonstrated that pain induced cerebral activities were found in the anterior insular cortex, anterior cingulate cortex, and amygdala. Several PET[168 169] and fMRI[170 171] studies also revealed that the perception of dyspnea could activate similar cortical regions in the brain. Moreover, lesions of the insular cortex can lead to reduced perceptive sensitivity of pain and dyspnea.[172] Lastly, since the insula, anterior insular cortex, and amygdala also process negative emotions, both the perception of dyspnea and pain can be affected by psychological factors, including emotion and attention.[173 174]

Recent clinical studies have also verified the theory of unpleasant symptoms.[161 162] The presence of dyspnea can increase the likelihood of having pain. Clark et al.[175] found that the prevalence of pain was 23% to 67% among participants with dyspnea, which was significantly higher than those without dyspnea. Similar results have been found in patients with COPD. For example, in a cross-sectional study that investigated multiple COPD symptoms, Borge et al.[22] concluded that pain intensity was positively correlated with dyspnea intensity. Also, Bentsen et al.[105] found that patients with COPD who reported pain had a significantly higher prevalence of dyspnea.

Taken all together, dyspnea is the most common symptom in patients with COPD and the presence of dyspnea appears to increase the occurrence of pain or aggravate the existing pain. Although the association between dyspnea and pain has been demonstrated, the relationship between pain and fatigue is not known.

1.4 Pain assessment tools and questionnaires utilized in COPD

Pain is subjective and is usually assessed by self-report measures, such as interviews and questionnaires, in clinical or research settings. Unfortunately, there is no standardized pain questionnaire that has been developed specifically for patients with COPD.[53] To date, investigations that evaluated pain in patients with COPD have used several self-reported assessment tools and questionnaires for pain, which are discussed in this section.

1.4.1 Numeric rating scale and visual analogue scale

The numeric rating scale and visual analogue scale are two pain assessment tools. The numeric rating scale primary assesses pain intensity in adults[176] and it has been widely used in

clinical settings because it can readily provide information on pain. An 11-point numeric rating scale is frequently used[177] in which 0 represents no pain and 10 represents maximal pain. Participants are asked to rate the intensity of pain by choosing a number between 0 to 10, inclusive.

The visual analogue scale is also used to evaluate pain intensity. A vertical or horizontal 10 cm line is used[178] that is typically anchored by "no pain" and the other end of the line (10 cm) is anchored by "maximal pain". Participants are asked to place an "X" or a perpendicular stroke that indicates their pain intensity along the length of the line.

1.4.2 Brief Pain Inventory

The BPI was initially developed for evaluating cancer-related pain[179] and has been translated into several different languages. In addition, the reliability and validity of the BPI have been established in varied medical conditions and clinical population, such as chronic non-malignant pain,[180] painful diabetic peripheral neuropathy,[181] osteoarthritis,[182] low back pain,[183] and postoperative pain.[184]

The BPI is composed of three components: (1) a body diagram; (2) the pain magnitude domain; and (3) the pain interference domain. Participants indicate pain locations on body diagrams and answer four questions on pain intensity and seven on how pain interferes with aspects of daily living using 0 to 10 numeric rating scales with 10 indicating the greatest pain severity and interference. Pain treatments and medications received as well as the amount of pain relief are also asked in the BPI. The BPI evaluates pain in the past 24 hours or the past week, depending on the purpose of its usage.

1.4.3 Short-Form McGill Pain Questionnaire

The MPQ is a well-established pain questionnaire that is used to evaluate chronic pain in adults.[185] The short-form MPQ was developed based on the MPQ in order to facilitate its use in clinical trials.[186] The reliability and validity of the short-form MPQ have been determined in patients with osteoarthritis,[187] rheumatoid arthritis,[188 189] fibromyalgia,[188] cancer,[190] chronic back pain,[191] and musculoskeletal pain.[189]

The short-form MPQ consists of three dimensions: (1) the sensory dimension; (2) the affective dimension; and (3) the present pain intensity. The sensory and affective dimensions include 11 and four words, respectively, that are used to describe pain. Participants rate each pain descriptor using a 4-point Likert scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). The present pain intensity is measured using a visual analogue scale and a 0 to 6 scale with descriptors of the present pain (0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating).

Among these pain assessment tools and questionnaires, the BPI is the most commonly used in studies of COPD patients.[49 50 62 65-67 69] However, the reliability and validity of these pain questionnaires, including the BPI, have not been established in patients with COPD, which is a gap that should be addressed in the realm of investigative pain studies in COPD.

1.5 Dissertation overview

Through the literature review of pain in COPD, several research questions remain to be answered. First, the reliability and validity of the questionnaires that are commonly used to evaluate pain in patients with COPD have not been established. Second, the comorbidities that

may cause pain and the association between pain and fatigue in COPD have not yet been examined. Third, the etiology of pain in patients with COPD is unclear. As a result, the overall purpose of this dissertation is to explore the pain experience, the contributors to pain, as well as potential causes of pain in patients with COPD.

This thesis dissertation consists of four studies as illustrated by the conceptual framework in Figure 1.1. Study I and Study II provided the methodological foundation for Study III. More specifically, Study I aimed to establish the reliability and validity of the BPI in patients with COPD. In a similar fashion, Study II aimed to establish the reliability and validity of the Brief Fatigue Inventory (BFI) and Dyspnea Inventory (DI) (two questionnaires with a parallel format to that of the BPI) in patients with COPD. The similar formats of the BPI, BFI and DI can facilitate more comparable evaluations among pain, dyspnea, and fatigue. In Study III, the questionnaires validated in Study I and Study II were used along with the questionnaires querying comorbidities that cause pain, quality of life, and self-efficacy. Together, these questionnaires were used to examine the pain experience; pain-related comorbidities; contributors to pain; and to compare pain, dyspnea, and fatigue in patients with COPD. The results of Study III were further investigated in Study IV, which was designed and conducted based on the findings of Study III. In Study IV, the etiology of trunk pain in patients with COPD was investigated using computed tomographic images of the thorax to examine thoracic vertebral deformity and arthropathy, two comorbidities that may cause pain in COPD.

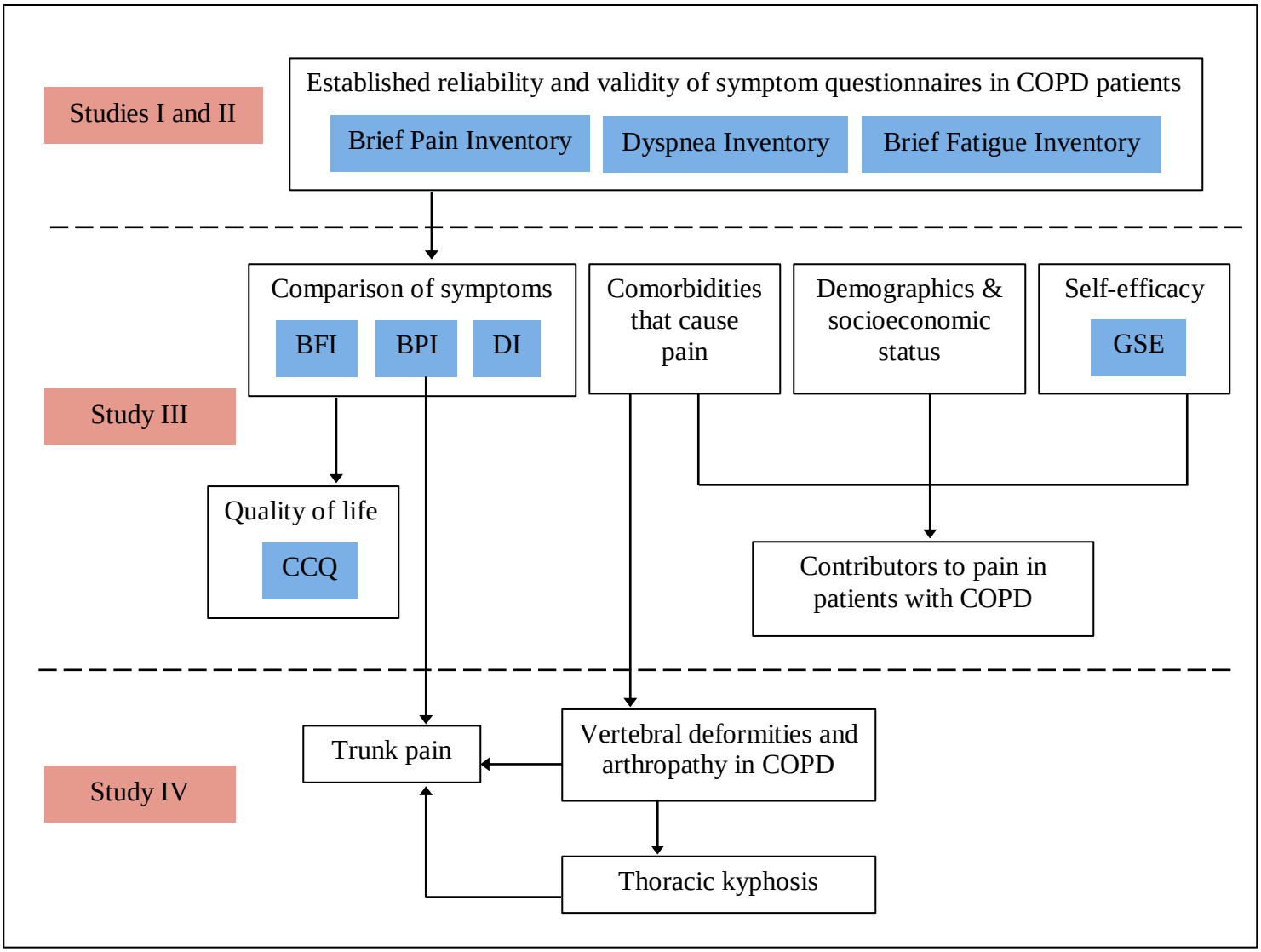

Figure 1.1 Conceptual framework of the dissertation that shows the flow of studies through the thesis

Abbreviations: BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; CCQ = Clinical COPD Questionnaire; DI = Dyspnea Inventory; GSE = General Self-efficacy Scale

1.6 Objectives and hypotheses

The overall hypothesis for this dissertation is that pain in patients with COPD is associated with musculoskeletal comorbidities and in particular, thoracic musculoskeletal abnormalities. To test this overall hypothesis, this dissertation is divided into four separate studies: to establish the reliability and validity of the pain, fatigue, and dyspnea questionnaires (Studies I and II); to survey self-reported contributors to pain together with comparisons of pain, dyspnea, and fatigue (Study III); and to examine if trunk pain is associated with thoracic vertebral deformity and arthropathy in patients with COPD (Study IV). The specific objectives and hypotheses of each study in this dissertation are stated below:

Study I: Reliability and Validity of the BPI in Patients with COPD (Chapter 2)

Objectives: To determine the reliability (internal consistency and test-retest reliability) and validity (convergent validity, divergent validity, discriminant validity, and construct validity) of the BPI in patients with COPD who attend pulmonary rehabilitation programs.

Hypotheses: The BPI will demonstrate high internal consistency and test-retest reliability. It will also exhibit convergent validity, construct validity, divergent validity, and discriminant validity that can discriminate the pain levels among COPD patients with different levels of physical activity and quality of life.

Study II: Reliability and Validity of the BFI and DI in Patients with COPD (Chapter 3)

Objectives: To determine the reliability (internal consistency and test-retest reliability) and validity (concurrent validity, discriminant validity, and construct validity) of the BFI and DI in patients with COPD who attend pulmonary rehabilitation programs.

Hypotheses: The BFI and DI will exhibit high internal consistency and test-retest reliability. They will demonstrate concurrent validity, construct validity, and discriminant validity that can discriminate the fatigue and dyspnea levels among patients with different levels of COPD severity.

Study III: Pain in Patients with COPD − A Survey Study (Chapter 4 and Chapter 5)

Objectives: (1) To determine the comorbidities that cause pain and the potential contributors to pain, including socioeconomic status, physical and psychological factors, and smoking history in patients with COPD (Chapter 4); (2) to compare pain, dyspnea, and fatigue, as well as examine the associations between pain and the other two symptoms (i.e. dyspnea and fatigue) using the questionnaires with a parallel format (Chapter 5); (3) to assess the impact of these three symptoms on quality of life (Chapter 5).

Hypotheses: Musculoskeletal conditions will be the most common type of comorbidity that contributes to pain in patients with COPD. Also, socioeconomic status, self-efficacy, and psychological conditions, and the levels of fatigue and dyspnea will be the contributors to pain (Chapter 4). The magnitude and interference scores of pain, dyspnea, and fatigue will not differ significantly and pain will be associated with dyspnea and fatigue. All these symptoms will negatively impact quality of life (Chapter 5).

Study IV: Etiology of Trunk Pain in Patients with COPD (Chapter 6 and Chapter 7)

Objectives: (1) To examine if patients with COPD have more trunk pain than current or ex-smokers without COPD (Chapter 6); (2) to determine whether thoracic vertebral deformity and

arthropathy are contributors to trunk pain in patients with COPD (Chapter 6); (3) to compare the prevalence of hyperkyphosis in patients with COPD and current or ex-smokers without COPD (Chapter 7); (4) to determine the associations between hyperkyphosis and trunk pain, thoracic vertebral deformity, and degenerative disc disease in patients with COPD (Chapter 7).

Hypotheses: Compared with non-COPD participants with a significant smoking history, patients with COPD will experience more trunk pain, which will be positively associated with vertebral deformity and arthropathy of intervertebral, costovertebral, and demi-facet joints (Chapter 6). Also, compared to those without COPD, patients with COPD will have greater thoracic kyphosis angles and a higher prevalence of hyperkyphosis, which will be associated with trunk pain, vertebral deformity, and degenerative disc disease (Chapter 7).

Chapter 2: Reliability and validity of the BPI in patients with COPD

2.1 Introduction

Pain is a commonly reported symptom in patients with COPD[53 54] with a reported prevalence that ranges from 38% to 82%.[26 29 62 63 65-68 70] Some of this variability in the prevalence of pain may be due to the heterogeneity of participants and the different measurement tools used among studies. More specifically, individuals with different cultural and ethnical backgrounds[57 58] may have different perceptual experiences of pain. Moreover, different pain instruments and definitions of pain could also contribute to a wide range of reported prevalence. Numerous tools have been implemented to explore experiences of pain, from unidimensional tools (e.g. visual analogue scale,[28] numeric rating scale,[21 105] and the Memorial Symptom Assessment Scale)[27 29] to multiple dimensional pain questionnaires, including the BPI[49 50 62 63 65-67 69] and MPQ.[49 66] Therefore, variability in participants' characteristics and measurement tools used in the studies may have contributed to the varied prevalence of pain among studies that investigated pain in patients with COPD.

A recent systematic review suggested that a standardized pain assessment tool in patients with COPD is required to provide an accurate prevalence.[53] However, to our knowledge, a pain assessment tool has not been specifically designed for patients with COPD. Among the currently developed pain instruments, the BPI appears to be a feasible measure to evaluate pain in patients with COPD given the fact that it has been used in at least eight studies to date.[49 50 62 63 65-67 69] The BPI was initially developed for assessing cancer-related pain,[179] and it has been used to assess pain extensively in different medical conditions.[180-183 192] However, in spite of its widespread use, the reliability and validity of the BPI in patients with COPD have not been formally established.

Therefore, the purpose of this study was to determine the reliability and validity of the BPI in patients with COPD. These attributes are essential psychometric properties for utilization of questionnaires, especially in a patient population that is different from whom the questionnaire is initially designed.

2.2 Methods

2.2.1 Study design and participants

This study consisted of two components: (1) a prospective study that recruited people with a primary diagnosis of COPD; and (2) a secondary analysis that retrieved the data from two previous studies that investigated pain in patients with COPD[49 50] (Figure 2.1). In addition to a primary diagnosis of COPD, the inclusion criteria for both components were: 50 years or older, no comorbidities that interfered with independent ambulation, sufficient English fluency, and no cognitive impairment that would interfere with answering the questionnaire.

The prospective study was performed to determine the test-retest reliability of the BPI. Patients with COPD who experienced pain were recruited from pulmonary rehabilitation programs at three sites (Vancouver General Hospital, St. Paul's Hospital, and New Westminster Pulmonary Rehab Clinic) in the greater Vancouver area, British Columbia and one site (Abilities Centre) in Whitby, Ontario. These participants were asked to complete the BPI twice one-week apart.

The secondary analysis component retrieved the de-identified data from two previously published studies.[49 50] The purposes of these two previously published studies were to compare the prevalence and characteristics of pain between patients with COPD and healthy individuals[49]

as well as to determine the relationships between pain and physical activity levels, quality of life, comorbidities,[49] and exercise capacity.[50] This current study collected the following data from patients with COPD: FEV_1% predicted, age, sex, and the item scores from four questionnaires (BPI, short-form MPQ, SF-36, and CHAMPS).

The Clinical Research Ethics Boards of the University of British Columbia and the University of Toronto approved this study. All participants provided written informed consent.

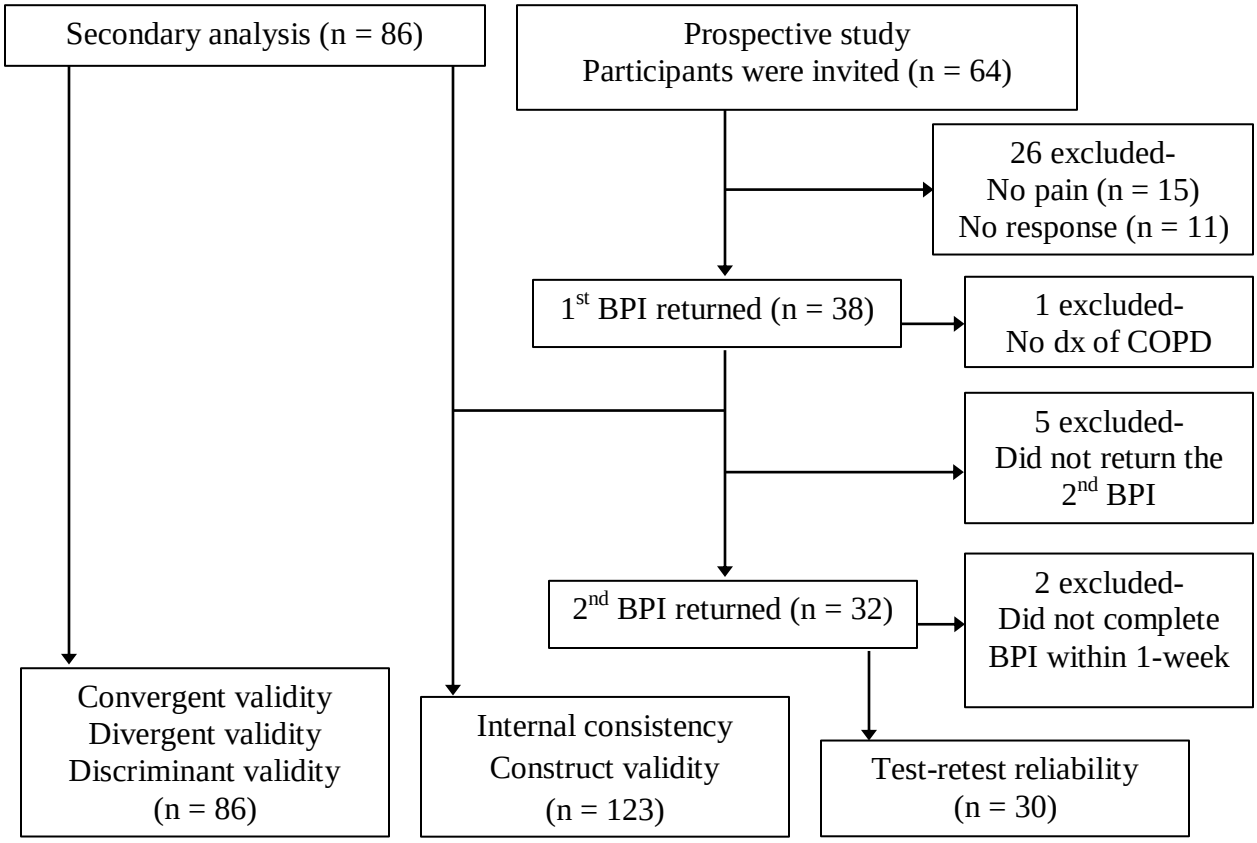

Figure 2.1 Study protocol and process

Abbreviations: BPI = Brief Pain Inventory; dx = diagnosis

2.2.2 Instruments

2.2.2.1 Brief Pain Inventory

The BPI[179] can provide information on pain locations, pain magnitude, and how pain interferes with aspects of daily living. Participants report pain locations by shading the location of pain and placing an "X" to indicate the area that hurts the most on a body diagram. The pain magnitude contains four items querying about pain magnitude in the following circumstances: "now", "the worst level", "the least level", and "on average". The items in the pain magnitude domain use 11-point numeric rating scales ranging from 0 (no pain) to 10 (pain as bad as you can imagine). The pain interference domain consists of seven items that ask about how pain interferes with "general activity", "mood", "walking ability", "normal work", "relations with other people", "sleep", and "enjoyment of life". Similar to the items in the pain magnitude domain, these seven items use 11-point numeric rating scales ranging from 0 (no interference) to 10 (completely interferes).

2.2.2.2 Short-form McGill Pain Questionnaire

The short-form MPQ[186] evaluates pain quality and pain magnitude. The pain quality domain consists of 11 sensory and four affective pain-related descriptors that are rated in intensity from 0 (none) to 3 (severe). The short-form MPQ total scores were calculated by adding scores from the sensory and affective domains. Pain magnitude is measured using a visual analogue scale that asks about pain intensity over the past week, and the Present Pain Intensity (PPI) that uses a Likert-scale from 0 (no pain) to 5 (excruciating). The short-form MPQ has shown to be an excellent tool to evaluate pain, with established reliability and validity among patients with chronic back pain.[191 193]

2.2.2.3 Medical Outcome Study Short Form-36

The SF-36 is a well-established health-related quality of life questionnaire.[194 195] It comprises 36 items that are distributed in eight domains: (1) physical functioning; (2) role limitations due to physical health; (3) general health perceptions; (4) vitality; (5) social functioning; (6) role limitation due to emotional health; (7) general mental health; and (8) bodily pain. Two scores are derived from the SF-36, i.e. the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score.

2.2.2.4 Community Health Activities Model Program for Seniors questionnaire

The CHAMPS questionnaire was developed to evaluate the outcome of the CHAMPS program for seniors,[196] and has been used to assess the physical activity levels in older adults.[197] It consists of 41 items that ask about the frequency and the amount of time the participants spend on various activities in one typical week during the past month. Caloric energy expenditure in exercise-related activities and the frequency of engagement in physical activities was determined from this questionnaire.

2.2.3 Statistical analysis

The internal consistency was assessed by Cronbach's alpha (α) coefficient. A Cronbach's α value of > 0.70 indicates a good correlation among the items.[198] The Cronbach's α coefficients were also calculated after an individual item in the BPI was omitted.

The test-retest reliability was determined by calculating intraclass correlation coefficients (ICCs) using a two-way mixed model. An ICC of > 0.75 indicates excellent test-retest reliability.[198] We performed an *a priori* sample size calculation to define the number participants

required for examining the test-retest reliability of the BPI. Since no study has been performed to validate the BPI in patients with COPD, we used the ICC from the previous studies[182 199] that determined the test-retest reliability of the BPI in patients with osteoarthritis and inflammatory bowel disease. An ICC of 0.9 was assumed and a sample size of > 25 could provide a power of 0.9, and an $\alpha_2 < 0.05$ with an acceptable ICC of at least 0.7.[200]

Convergent and divergent validity were determined by examining the correlations between the BPI and the SF-MPQ scores as well as the BPI scores and each domain of the SF-36 scores, respectively, using Spearman rank correlation coefficients. A correlation coefficient > 0.75 represents a high correlation.[198] Construct validity was assessed through factor analysis using a principal axis factor analysis with direct Oblimin rotation.[198] Lastly, discriminant validity was examined by determining the associations between the SF-36 and the BPI scores as well as the CHAMPS scores and the BPI scores, respectively, using linear regression analysis. All statistical analyses were performed using the SPSS software package (Version 22.0, Armonk, NY: IBM Corp). A *p*-value < 0.05 was set to indicate significant differences.

2.3 Results

2.3.1 Participants

For the prospective component of this study, 64 participants were invited and 53 returned the questionnaires (response rate = 83%). Of the respondents, 15 reported no pain and one participant did not meet the inclusion criteria and, therefore, were excluded from the data analysis (Figure 2.1). In total, 32 of 37 participants returned both the questionnaires. Two of the participants completed the BPI beyond an acceptable test-retest interval (17 and 56 days,

respectively). Thus, data of 30 participants were included in the analysis of test-retest reliability. In addition, data was retrieved from 86 subjects for the secondary analyses. Demographic characteristics of the participants are presented in Table 2.1.

Table 2.1 Demographic characteristics of the participants

	Secondary analysis (n = 86)	Prospective component (n = 37)	Test-retest reliability (n = 30)	Total (n = 123)
Sex; n (%)				
Male	43 (50%)	25 (68%)	19 (63%)	68 (55%)
Female	43 (50%)	12 (32%)	11 (37%)	55 (45%)
Age	71.4 (8.6)	68.7 (7.8)	68.3 (7.6)	70.6 (8.5)
FEV_1	46.8 (16.9)	48.9 (16.5)	46.3 (16.3)	47.5 (16.7)

Data are presented as mean (SD) unless specified.

Abbreviation: FEV_1 = forced expiratory volume in one second

2.3.2 Internal consistency

Cronbach's α coefficients for the four BPI magnitude items and seven BPI interference items were 0.91 and 0.94, respectively, showing an excellent internal consistency in the magnitude and interference domains of the BPI. Table 2.2 presents the values of Cronbach's α coefficients when the item was deleted.

Table 2.2 Internal consistency of the BPI

	Cronbach's α if item deleted
BPI magnitude domain (Cronbach's α = 0.91)	
Worst pain	0.89
Least pain	0.90
Average pain	0.86
Present pain	0.89
BPI interference domain (Cronbach's α = 0.94)	
General activity	0.92
Mood	0.93
Walking ability	0.93
Normal work	0.93
Relations	0.93
Sleep	0.93
Enjoyment of life	0.92

Abbreviation: BPI = Brief Pain Inventory

2.3.3 Test-retest reliability

Table 2.3 presents the ICCs for each item in the BPI. The mean test-retest interval was 6.9 ± 1.8 days in 30 patients with COPD. Overall, the BPI total scores demonstrated excellent test-retest reliability (ICC = 0.93, 95% CI = 0.86 − 0.97). The ICCs of the BPI magnitude and interference domains were 0.76 (95% CI = 0.54 − 0.88) and 0.92 (95% CI = 0.85 − 0.96),

respectively, which indicated excellent test-retest reliability for these two domains of the BPI. Among the eleven items of the BPI, all the items demonstrated good to excellent test-retest reliability[201] with the ICCs ranging from 0.67 to 0.85.

Table 2.3 Test-retest reliability of the BPI (n = 30)

	First test Mean (SD)	Second Test Mean (SD)	ICC (3,1) (95% CI)
Worst pain	5.9 (1.6)	6.3 (1.7)	0.72 (0.48, 0.86)
Least pain	2.3 (1.9)	2.7 (1.9)	0.81 (0.63, 0.90)
Average pain	4.1 (1.6)	4.3 (1.6)	0.75 (0.54, 0.88)
Present pain	3.3 (2.3)	4.1 (2.3)	0.67 (0.39, 0.83)
General activity	4.0 (2.5)	4.6 (2.3)	0.74 (0.51, 0.87)
Mood	3.7 (2.9)	3.4 (2.7)	0.85 (0.71. 0.92)
Walking ability	4.7 (2.8)	4.7 (2.8)	0.73 (0.49, 0.86)
Normal work	4.6 (2.4)	4.9 (2.6)	0.83 (0.68, 0.92)
Relations	2.8 (3.0)	2.8 (2.5)	0.82 (0.65, 0.91)
Sleep	4.6 (3.2)	4.1 (2.9)	0.82 (0.64, 0.91)
Enjoyment of life	5.2 (3.0)	4.9 (2.4)	0.83 (0.65, 0.92)
Magnitude score	3.9 (1.4)	4.3 (1.6)	0.76 (0.54, 0.88)
Interference score	4.2 (2.3)	4.1 (2.2)	0.92 (0.85, 0.96)
Total score	4.1 (1.9)	4.2 (1.9)	0.93 (0.86, 0.97)

2.3.4 Construct validity

The factor analysis yielded a two-factor solution in the BPI. The eigenvalue of the first factor was 7.34, which explained 66.7% of the variance in the BPI. The eigenvalue for the second factor was 1.15 that explained an additional 10.4% of the variance in the BPI. Overall, these two factors explained 77.1% of the total variance. Four items of the BPI were loaded onto

the first factor, which was related to pain intensity. Seven items of the BPI were loaded onto the second factor related to pain interference (Table 2.4).

Table 2.4 Factor loadings for items of the BPI (n = 123)

	Factor	
	Magnitude	Interference
Worst pain	**0.58**	0.34
Least pain	**0.90**	-0.10
Average pain	**0.90**	0.03
Present pain	**0.72**	0.16
General Activity	0.07	**0.85**
Mood	-0.003	**0.81**
Walk	-0.07	**0.92**
Work	0.03	**0.83**
Relations	-0.05	**0.82**
Sleep	0.24	**0.59**
Enjoyment	0.03	**0.89**

* The bold font indicates the items were loaded onto the factor. The normal font indicates that the items were not highly correlated with the factor.

2.3.5 Convergent validity

Table 2.5 presents the Spearman's correlation coefficients between the BPI and short-form MPQ. The convergent validity between the BPI total score and short-form MPQ total score was high with the correlation coefficients of being 0.79 ($p < .001$). The correlation between the BPI magnitude score and the SF-MPQ sensory score was good ($\rho = 0.72$). The BPI demonstrated

high concurrent validity with the short-form MPQ visual analogue scale. Also, the items querying present pain intensity in the BPI was highly correlated with the short-form MPQ PPI.

Table 2.5 Convergent validity of the BPI and short-form MPQ (Spearman correlation coefficient)

		Short-form MPQ			
		Sensory	Total score	VAS	PPI
BPI	Magnitude score	0.72**		0.86**	
	Interference score			0.82**	
	Total score		0.79**	0.88**	
	BPI present pain score				0.78**

** *p*-value < 0.001

Abbreviations: BPI = Brief Pain Inventory; MPQ = McGill Pain Questionnaire; PPI = Present Pain Intensity; VAS = visual analogue scale

2.3.6 Discriminant validity

The discriminant validity of the BPI was examined in COPD patients with different levels of quality of life and physical activity. The BPI total scores were negatively associated with the SF-36 PCS scores ($F_{1, 84} = 19.3$, $p < 0.001$). Similarly, the BPI total scores were negatively associated with the caloric energy expenditure in physical activity ($F_{1, 84} = 4$, $p < 0.05$) and the frequency of engagement in physical activity ($F_{1, 84} = 4.3$, $p < 0.05$) (Table 2.6).

Table 2.6 The associations of the SF-36 and BPI scores as well as the CHAMPS and BPI scores

Variable	Regression coefficient (95% CI)	Standard error
PCS score of the SF-36	-0.12 (-0.17, -0.06)*	0.03
MCS score of the SF-36	-0.03 (-0.06, 0.005)	0.02
Energy expenditure (1000 kcal/week)	-0.3 (-0.6, -0.004)*	0.2
Frequency of physical activity (score/week)	-0.05 (-0.09, -0.003)*	0.02

* *p*-value < 0.05

Abbreviations: PCS = Physical Component Summary; MCS = Mental Component Summary

2.3.7 Divergent validity

The divergent validity was examined by calculating the correlations between the BPI and each domain of the SF-36 using Spearman correlation. The correlations between the BPI total score and all the SF-36 domains were low (ρ= -0.22 to -0.31), except for bodily pain (ρ= -0.54) (Table 2.7).

Table 2.7 Divergent validity of the BPI and SF-36

		BPI		
		Magnitude	Interference	Total score
SF-36	Physical functioning	-0.14	-0.34**	-0.29**
	Role- physical	-0.09	-0.26*	-0.22*
	General health perceptions	-0.24*	-0.32*	-0.31**
	Vitality	-0.15	-0.26*	-0.23*
	Social functioning	-0.13	-0.24*	-0.22*
	Role- emotional	-0.11	-0.26*	-0.22*
	General mental health	-0.09	-0.28*	-0.22*
	Bodily pain	-0.42**	-0.53**	-0.54**

*p-value < 0.05; **p-value < 0.01

Abbreviations: BPI = Brief Pain Inventory; SF-36 = Medical Outcome Study Short Form-36

2.4 Discussion

This study established the reliability and validity of the BPI in patients with COPD. The major findings were that the BPI demonstrated high internal consistency and test-retest reliability in patients living with COPD. Construct validity was determined and showed that the items in the BPI magnitude and interference domains measure the intended constructs. The BPI had good convergent validity with another well-established pain questionnaire, the SF-MPQ. Divergent validity analysis revealed that the BPI and the SF-36 domains, except for the bodily pain domain of the SF-36, assess different constructs. Lastly, the BPI possesses the discriminant validity that

can distinguish pain levels among COPD patients with different quality of life and physical activity levels.

The high internal consistency of the magnitude and interference domains of the BPI reflects that the items in each domain measure the same respective concept, i.e. the amount of pain and how pain interferes with aspects of daily living. Moreover, this study examined if deleting any of the individual items in the two domains could change the internal consistency. The results showed that deleting any individual item could produce a lower Cronbach's α value than the Cronbach's α coefficients of the BPI magnitude and interference domains in their entirety (Table 2.2). Thus, these data indicate that all the items in the two domains should be retained in the BPI when evaluating pain in patients with COPD.

The one-week test-retest reliability of the BPI in patients with COPD was high. Previous studies have examined the test-retest reliability of the BPI with an interval between 1 to 10 days.[182 202-204] It is expected that shorter test-retest intervals may increase reliability due to memory effects whereas longer test-retest intervals may lead to lower values of ICCs because of potential changes in symptoms.[182 198] There is no rule of thumb regarding the test-retest intervals. Therefore, an interval of one week was chosen to avoid carryover memory effects and to minimize potential dramatic changes in the underlying causes that might influence pain. In order to control for the effects of medications or treatments on pain, we asked participants to list the pain treatments and medications received as well as the amount of pain relief. The ICC of the amount of pain relief (ICC = 0.87, 95% CI = 0.73 − 0.94) indicated that the pain treatments or medications that participants have received during the study did not affect the test scores. In addition, we found that the value of ICC for the "present pain" item was lower (ICC = 0.67),

which is consistent with the previous studies.[203 205] The present pain intensity has been shown to change when testing at two or more intervals and as expected, appears to greatly depend on participants' perception of pain at the moment when completing the BPI. In spite of a lower ICC, the value of 0.67 is deemed as good reliability.[201] Therefore, the overall test-retest reliability of the BPI in patients with COPD can be considered good to excellent.

The results of this study suggested that the eleven items in the BPI can be grouped into two factors that are consistent with their domain: pain magnitude and pain interference. This finding is similar to the data from the previous BPI validation studies in different patient populations e.g. cancer pain, low back pain, and chronic pain.[180 183 203 206] The factor loadings of all the 11 items (Table 2.4) showed that the four items in the magnitude domain were related to each other and represented the construct of pain intensity. Similarly, all seven items in the interference domain reflected the same construct, i.e. how pain interfered with aspects of daily living. Therefore, the items in the BPI have the ability to measure the intended constructs.

The convergent validity of the BPI was determined by its comparison with the SF-MPQ. The correlation between the BPI magnitude score and the SF-MPQ sensory score was considered to be good ($\rho = 0.72$). The slightly lower rho values may be due to the different pain properties that the two questionnaires aim to measure. Although the BPI magnitude domain also measures the sensory aspects of pain, the four BPI magnitude items focus more on the severity of pain. In contrast, the SF-MPQ sensory domain contains pain characteristics as defined by descriptors and the severity of each pain descriptor is rated.[186] It is possible that a person who reports a higher pain severity score on the BPI may not find the descriptors that can adequately describe pain on the SF-MPQ and, thus, results in a lower sensory domain score. Despite the somewhat different

traits of pain that are derived from these two questionnaires, the underlying construct of the BPI and SF-MPQ is similar. The high correlations between the BPI present pain scores and the SF-MPQ PPI as well as the BPI total scores and the SF-MPQ total scores indicated that the two questionnaires reflect the same primary construct - pain.

This study found that the BPI can discriminate the levels of pain among COPD patients with different levels of quality of life and physical activity. This is clinically important as increased pain has been reported to be associated with physical inactivity[50] and poor quality of life[65] in patients with COPD. We did not group participants based on their quality of life or physical activity because there are no established thresholds to categorize the scores of the SF-36 and CHAMPS as good and poor quality of life or high and low physical activity levels, respectively. Moreover, we only found that the BPI has the ability to distinguish pain levels among COPD patients with varied SF-36 PCS scores but not MCS scores. Reasons why the BPI lacks the discriminant validity in COPD patients with different SF-36 MCS scores are unclear. However, previous studies have found that the impact of pain on the physical component of quality of life is greater than that on the mental component.[207-209] Pain may have a more immediate, direct effect on physical-related quality of life whereas it might have a more gradual and/or complex impact on mental-related aspects that affect quality of life.[209]

This study has a couple of limitations. First, we recruited participants with COPD from pulmonary rehabilitation programs. However, data retrieved from two previous studies[49 50] for our secondary analysis included patients with COPD from pulmonary rehabilitation programs and respirologists' clinics. Thus, the generalizability of the results of this study to other groups of patients with COPD might be limited. A second limitation is that this study did not examine the

responsiveness of the BPI in patients with COPD. Therefore, the ability of the BPI to detect changes after a particular intervention in patients with COPD remains to be determined.

2.5 Conclusions

The BPI is not only the most commonly used pain questionnaire in COPD studies, it also provides information on pain locations, pain magnitude and how pain interferes with various aspects of daily life activities. This study formally established the reliability and validity of the BPI in patients with COPD, which can provide strong evidence that the assessment results from this pain questionnaire are reliable and valid. Lastly, it is worthwhile to investigate the responsiveness of the BPI in patients with COPD in the future in order to broaden evidence for its psychometric properties.

Chapter 3: Reliability and validity of the BFI and DI in patients with COPD

3.1 Introduction

COPD is projected to become the third leading cause of death by 2030[210] and imposes a substantial economic burden on medical systems and individuals.[3 211] Patients with COPD are most often limited by dyspnea and fatigue,[3] which are considered to be primary limitations to exercise[212] and physical activity[213] as well as predictors of higher mortality.[214 215] More recently, pain has been shown to affect the majority of patients with COPD and is a contributor to poor physical performance.[54]

Because of the high prevalence of these three symptoms in COPD, their assessment is essential in the management of COPD.[3] However, to date, there are no studies that compare the relative severity of pain, dyspnea and fatigue in COPD. The only study that attempts to quantify these symptoms is a Japanese study, which used the BPI, the BFI, and the DI in lung cancer patients.[216]

The BPI, BFI, and DI, which use parallel descriptors and numeric scales, could provide more readily comparable scores of symptom severity and interference. The BPI appears to be a feasible pain measurement tool because studies have shown good reliability[179 180 192 205] and validity in people with pain due to cancer,[179 205] nonmalignant causes,[180 192] and COPD.[49] Although the BFI has not been tested in patients with COPD, good test-retest reliability, construct validity, and concurrent validity have been shown in cancer patients.[217] Although the DI is only reported in one study,[216] its similar format will allow comparisons to the severity and interference scores of the BPI and BFI.

One of the most well validated and commonly used questionnaires to evaluate fatigue and dyspnea in COPD is the CRQ.[218-220] However, in spite of the strengths of the CRQ, no single item asks about pain. Further, the phrasing and Likert scoring of its items severely limit any relative comparisons to the BPI or other established pain questionnaires. Moreover, using the lengthy CRQ plus another questionnaire that evaluates pain in COPD could cause substantial "questionnaire fatigue". Thus, for clinical and research purposes, short questionnaires with a similar format would have great advantages over a longer questionnaire, such as the CRQ, plus a pain questionnaire. Therefore, the purpose of this study was to determine the reliability and validity of the BFI and DI in patients with COPD.

3.2 Methods

3.2.1 Study design and participants

This study collected both retrospective and prospective data (Figure 3.1). The inclusion criteria were patients with COPD (confirmed with spirometry) aged 45 years and older with English fluency and no cognitive impairment that impeded the ability to provide informed consent.

Retrospective data were retrieved from the charts of patients with COPD who attended the pulmonary rehabilitation program at Vancouver General Hospital in Vancouver, Canada. Data retrieved included FEV_1, age, sex, and scores for the questionnaires (CRQ, BFI, and DI). The pulmonary rehabilitation program at Vancouver General Hospital used the self-administrated CRQ with an individualized dyspnea domain (CRQ-SAI).

For the prospective component, participants were recruited from the pulmonary rehabilitation programs at four sites: Vancouver General Hospital, Richmond Hospital, Langley Memorial Hospital, and Jim Pattison Outpatient Care and Surgery Center, in the greater Vancouver area, Canada. Participants received a survey package containing: a consent form, CRQ, BFI, and DI. The CRQ with a standardized dyspnea domain (CRQ-SAS) was used in this group of participants. Participants were asked to complete these three questionnaires on the same day. The estimated completion time was 20 to 30 minutes. One week later, they were provided a second package that contained the BPI, DI, and a screening question that asked about a change in their COPD status. The estimated completion time was 10 to 15 minutes. The study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants provided written informed consent.

Validity of the BFI and DI was examined combining retrospective and prospective data from the CRQ, BFI and DI (Figure 3.1). Concurrent validity was determined separately using the retrospective and prospective data, respectively, because different versions of the CRQ were used in the two settings as described previously. Test-retest reliability of the BFI and DI was examined from the first and second packages of the BFI and DI in the prospective component.

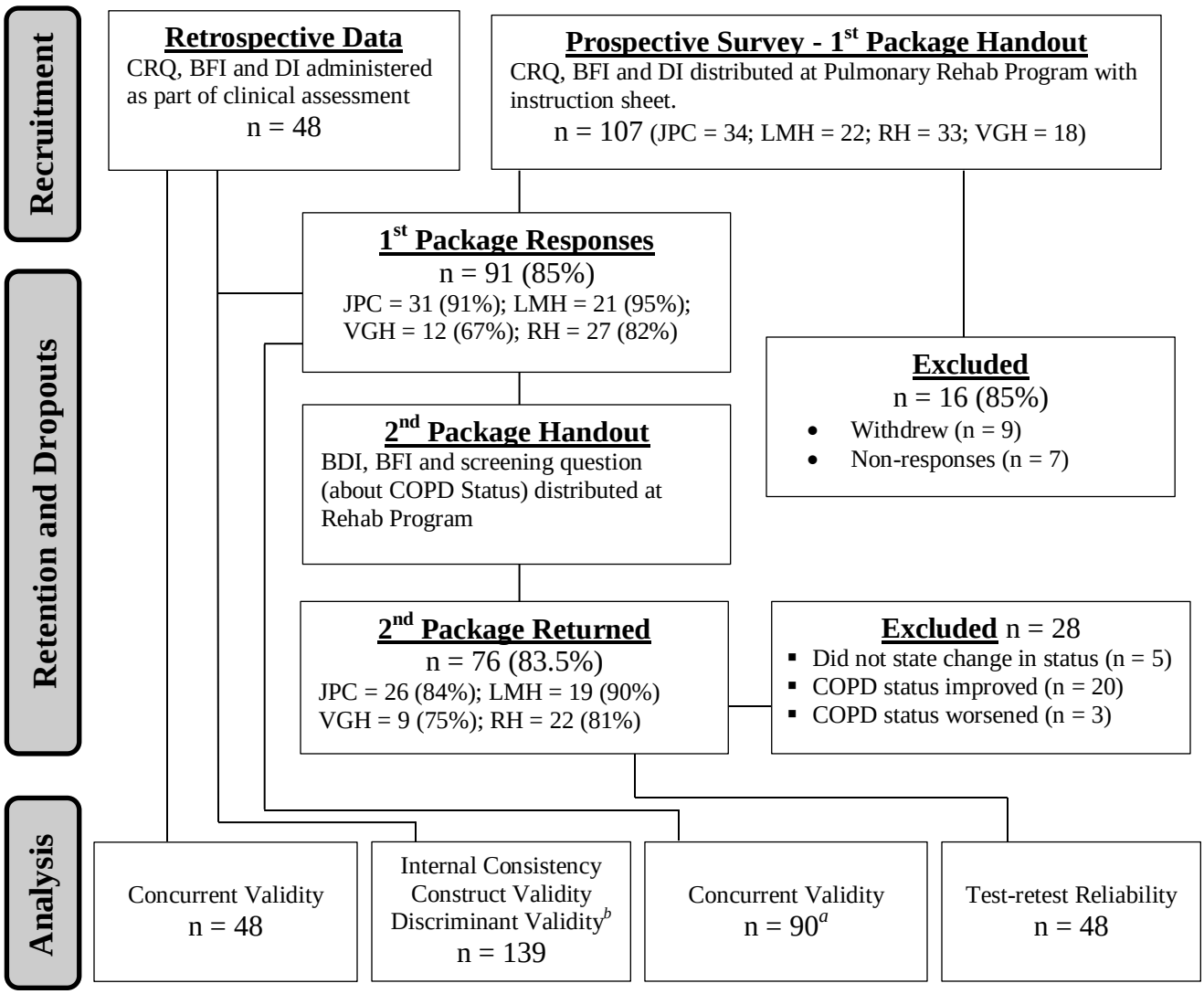

Figure 3.1 The summary of the study process

Abbreviations: CRQ = Chronic Respiratory Questionnaire; DI = Dyspnea Inventory; BFI = Brief Fatigue Inventory; JPC = Jim Pattison Outpatient Care and Surgery Centre; LMH = Langley Memorial Hospital; RH = Richmond Hospital; VGH = Vancouver General Hospital; COPD = chronic obstructive pulmonary disease

[a] One participant was excluded due to not able to complete all questionnaires on the same day

[b] Discriminant validity was assessed in 137 participants

3.2.2 Instruments

3.2.2.1 Chronic Respiratory Questionnaire

Concurrent validity of the BFI and DI was determined by using the CRQ as a criterion measure. The CRQ contains four domains - dyspnea (five items), fatigue (four items), emotional function (seven items), and mastery (four items). A seven-point Likert scale is used for each question, with a higher score indicating a better outcome. CRQ-SAI requires participants to elicit activities that make them most short of breath; CRQ-SAS asks about the degree of dyspnea when performing a standardized list of activities.

3.2.2.2 Brief Fatigue Inventory

The BFI consists of 10 items. The first item asks if participants have experienced fatigue in the last week (yes or no). Three items query fatigue magnitude “now”, “usual level”, and “worst level”, respectively via numeric rating scales that are anchored by 0 (no fatigue) to 10 (as bad as you can imagine). Fatigue interference is evaluated by six items with numeric rating scales anchored by 0 (does not interfere) to 10 (completely interferes).

3.2.2.3 Dyspnea Inventory

The DI consists of 11 items with a parallel format to the BFI. The first item asks if participants have experienced dyspnea in the last week (yes or no) followed by three items that query dyspnea magnitude using similar descriptors to the BFI via 10-point numeric rating scales. Dyspnea interference is evaluated by seven items via numeric rating scales. The interference domain of the DI has one additional item that asks about sleep, which is not contained in the interference domain of the BFI.

3.2.3 Statistical analysis

The internal consistency was assessed by Cronbach alpha (α) coefficient. A Cronbach α greater than 0.70 indicates a good correlation.[198] The test-retest reliability was examined by ICCs using a two-way mixed model. An ICC greater than 0.70 represents high test-retest reliability.[198] To eliminate bias due to fluctuation in disease severity, prospective data to examine test-retest reliability of the BFI and DI were used only if the participants reported that their COPD status did not change between completion of the first and second survey packages.

Concurrent validity was determined by examining the correlation between the CRQ and the target questionnaires using Spearman rank correlation. A correlation coefficient value greater than 0.75 represents high concurrent validity.[198] Construct validity was assessed through factor analysis with a principal axis factor analysis that is a common method of determining construct validity.[198] Factor analysis examines correlations among factors and each item of questionnaires. Discriminant validity was determined by comparing BFI and DI scores among participants with different disease severity using one-way ANOVA. Disease severity was defined using GOLD criteria.[3] All statistical analyses were performed using SPSS (Version 22.0, Armonk, NY: IBM Corp). A p-value < 0.05 was set to indicate significant differences.

3.3 Results

3.3.1 Participants

In the prospective component, 91 of 107 recruits returned the first questionnaire packages; of those responders, 76 returned the second package (Figure 3.1). The retrospective data consisted of 48 eligible patients with a complete set of questionnaires. The demographic

characteristics of the retrospective and prospective components showed similar age (p = 0.31), and disease severity (p = 0.33) (Table 3.1).

Table 3.1 Demographic characteristics of participants

	Prospective; Mean (SD)		Retrospective; Mean (SD)		Total; Mean (SD)	
Age (years)	71.4 (8.3)		69.5 (10.7)		70.7 (9.2)	
FEV_1 (% predicted)	51.7 (18.0)		54.7 (18.0)		52.7 (8.0)	
	n	%	n	%	n	%
	Sex					
Male	48	52.7	28	58.3	76	54.7
Female	43	47.3	20	41.7	63	45.3
	COPD severity					
Mild	5	5.5	4	8.3	9	6.5
Moderate	44	48.3	25	52.1	69	49.6
Severe	29	31.9	13	27.1	42	30.2
Very severe	11	12.1	6	12.5	17	12.2

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second

3.3.2 Internal consistency

Cronbach α coefficients for the nine BFI items and 10 DI items were 0.96 and 0.96, respectively, which indicated excellent internal consistency for both questionnaires in patients with COPD (n = 139).

3.3.3 Test-retest reliability

Of the 76 participants who returned the second package, 28 were excluded because of a change in COPD status or for not completing the screening question (Figure 3.1), which provided complete data for 48 participants.

The BFI and DI total scores showed high test-retest reliability ($ICC_{3,1}$ = 0.86 and 0.91, respectively; Table 3.2). The magnitude and interference domains of the BFI and DI also demonstrated high test-retest reliability ($ICC_{3,1}$ = 0.87 and 0.82 for magnitude and interference domains of the BFI; $ICC_{3,1}$ = 0.87 and 0.90 for magnitude and interference domains of the DI, respectively; Table 3.2). The ICCs reflective of test-retest reliability of each item of the BFI and DI are presented in Table 3.2 and ranged from 0.74 to 0.95.

Table 3.2 Test-retest reliability (n = 48)

Item	First test Mean (SD)	Second test Mean (SD)	ICC (3,1) (95% CI)
BFI			
Fatigue now	3.46 (2.59)	3.33 (2.60)	0.89 (0.81,0.94)
Fatigue usual	3.71 (2.40)	3.65 (2.43)	0.83 (0.72,0.90)
Fatigue worst	4.75 (2.75)	4.83 (2.73)	0.74 (0.58,0.85)
General activity	4.02 (2.84)	3.85 (2.76)	0.79 (0.65,0.88)
Mood	3.02 (2.44)	2.90 (2.43)	0.74 (0.58,0.85)
Walking ability	4.21 (3.08)	3.96 (3.01)	0.80 (0.67,0.88)
Normal work	4.94 (3.27)	4.46 (3.02)	0.79 (0.65,0.88)
Relations	3.23 (3.02)	2.69 (2.55)	0.75 (0.59,0.85)
Enjoyment of life	3.90 (2.96)	3.31 (2.74)	0.77 (0.62,0.87)
BFI Magnitude	3.97 (2.46)	3.94 (2.44)	0.87 (0.77,0.92)
BFI Interference	3.89 (2.66)	3.53 (2.53)	0.82 (0.70,0.89)
BFI Total	3.92 (2.51)	3.66 (2.43)	0.86 (0.77,0.92)
DI			
Dyspnea now	2.29 (2.40)	2.38 (2.38)	0.76 (0.61,0.86)
Dyspnea usual	3.40 (2.43)	3.29 (2.32)	0.77 (0.63,0.87)
Dyspnea worst	5.19 (2.76)	5.13 (2.71)	0.83 (0.71,0.90)
General activity	3.83 (2.72)	4.00 (3.04)	0.80 (0.67,0.88)
Mood	2.56 (2.56)	2.50 (2.47)	0.86 (0.77,0.92)
Walking ability	4.23 (2.94)	4.19 (2.91)	0.81 (0.69,0.89)

Item	First test Mean (SD)	Second test Mean (SD)	ICC (3,1) (95% CI)
Normal work	4.72 (2.99)	4.36 (2.96)	0.82 (0.70,0.90)
Relations	2.56 (2.80)	2.58 (2.70)	0.87 (0.77,0.92)
Sleep	2.19 (2.86)	2.13 (2.81)	0.95 (0.91,0.97)
Enjoyment of life	3.52 (2.98)	3.31 (2.77)	0.80 (0.67,0.88)
DI Magnitude	3.63 (2.28)	3.60 (2.22)	0.87 (0.78,0.93)
DI Interference	3.37 (2.52)	3.30 (2.52)	0.90 (0.83,0.94)
DI Total	3.44 (2.39)	3.39 (2.41)	0.91 (0.85,0.95)

Abbreviations: BFI = Brief Fatigue Inventory; CI = confidence interval; DI = Dyspnea Inventory; ICC = intraclass coefficient correlation

3.3.4 Concurrent validity

The concurrent validity of the BFI and DI was high when comparing to the CRQ-SAS (ρ = -0.83, -0.78, respectively, $p < 0.01$). The retrospective data, compared to the CRQ-SAI, demonstrated high concurrent validity for the BFI (ρ = -0.83, $p < 0.01$) and moderate concurrent validity of the DI (ρ = -0.57, $p < 0.01$).

3.3.5 Construct validity

The Kaiser-Meyer-Olkin measure of sampling adequacy revealed values of 0.93 and 0.94 for the BFI and DI, respectively, which suggested that the items of the two questionnaires were factorable. The factor analyses yielded a one-factor solution in both questionnaires. The first factor explained 78.3% and 75% of the variance in the BFI and DI, respectively. The factor

loadings in the BFI and DI were high, which indicated the items of each questionnaire represented the same construct (Table 3.3).

Table 3.3 Factor loadings for items of the BFI and DI (n = 139)

Item	Factor loading	
	BFI	DI
Symptom now	0.79	0.76
Symptom usual	0.86	0.84
Symptom worst	0.82	0.83
General activity	0.93	0.92
Mood	0.88	0.87
Walking ability	0.86	0.87
Normal work	0.91	0.89
Relations	0.86	0.86
Sleep	N/A	0.77
Enjoyment of life	0.90	0.88
Eigenvalues	7.05	7.50
Total variance (%)	78.3%	75%

Abbreviations: BFI = Brief Fatigue Inventory; DI = Dyspnea Inventory

3.3.6 Discriminant validity

There was a significant difference of the DI score among people with different COPD severity ($F_{3,133} = 2.89$, $p = 0.04$). Post hoc tests using Tukey HSD showed that the mean DI score

in people with moderate COPD was significantly lower than that in people with very severe COPD (Table 3.4). However, the BFI score did not show any significant difference among people with different COPD severity.

Table 3.4 BFI and DI among participants with COPD

Questionnaire	Mild (n = 9)	Moderate (n = 69)	Severe (n = 42)	Very severe (n = 17)	*p*-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
BFI	3.53 (2.51)	3.84 (2.31)	3.83 (2.86)	5.14 (2.37)	0.24
DI	2.94 (2.25)	3.37 (2.22)*	3.69 (2.54)	5.16 (2.63)*	< 0.05

*Significant difference existed between groups

Abbreviations: BFI = Brief Fatigue Inventory; DI = Dyspnea Inventory

3.4 Discussion

This study demonstrated good reliability of the BFI and DI in patients with COPD as reflected by excellent internal consistency as well as high test-retest reliability. In addition, the BFI and DI had moderate to high concurrent validity with different versions of the CRQ. The examination of construct validity provides evidence that items of the BFI and DI measure the intended symptoms, that is, fatigue and dyspnea, respectively.

Both the BFI and DI presented excellent internal consistency in magnitude and interference domains, which indicates that the items in the same domain measure the same concept. Also, the test-retest reliability was high for the BFI and DI. The interval between tests can influence reliably because a short interval may overestimate values due to recall, whereas a longer interval may underestimate this property due to fluctuation in disease status.[198] In

previous studies that examined test-retest reliability of questionnaires in COPD, researchers used different time intervals, ranging from one day to four weeks.[218 221-223] Therefore, this study used a one-week interval to minimize carryover effects and potential COPD status changes. Bias due to fluctuations in disease status was further controlled for by asking participants to provide a self-report of whether their condition changed.

This study used the CRQ as the criterion measure because it is a widely used questionnaire with well-established psychometric properties that can assess both dyspnea and fatigue in COPD.[220 224] Unlike the BFI, the concurrent validity of the DI ranged between moderate to good. The discrepancy between the validity levels of the DI is likely related to the difficulty and potential similarities of dyspnea items identified in the CRQ-SAI. The CRQ-SAI requires participants to identify five activities that elicit the most dyspnea from a list[225] whereas the CRQ-SAS provides participants with five predetermined activities to rate dyspnea.[226] The CRQ-SAI requires more time to complete and many participants cannot identify five activities.[226] Indeed, our retrospective data showed that 21% of participants (n = 10) did not select five activities. The CRQ-SAI also provides the opportunity to select items that are similar while such activities might fit within one term on the predetermined list of the CRQ-SAS. For example, having a bath or shower, eating, and dressing (from the CRQ-SAI) can be grouped into "taking care of your basic needs" in the CRQ-SAS. Our retrospective data demonstrated that 75% of participants (n = 36) identified more than two walking activities in its dyspnea domain. The similarity of activities in the CRQ-SAI and fewer items identified likely provide an explanation for the lower correlations and concurrent validity of the DI with this measure.

Neither the DI nor BFI discriminated the dyspnea and fatigue levels among people with different COPD severities. The primary explanation is that this study used GOLD criteria[3] to classify COPD severity, which mainly relies on the level of airflow limitation (FEV_1). It has been previously reported that FEV_1 is poorly related to COPD symptoms, including dyspnea and fatigue.[3 227] and that people with severe COPD may have mild symptoms and vice versa. In addition, the primary focus of both questionnaires is not to discriminate the disease severity of patients with COPD but rather to evaluate symptom severity and interference.

Pain, dyspnea, and fatigue are multidimensional and subjective sensations.[228-230] Both pain and dyspnea are alerting sensations[231] and the perceptions of pain and dyspnea can stimulate similar cortical regions of brains, such as the anterior insular cortex, anterior cingulate cortex and amygdala.[171 172] Furthermore, because pain and dyspnea share a similar emotion-related brain network that presents analogous negative affect states, they can be influenced by psychological factors, for example, emotion and attention.[232] Compared to pain and dyspnea, factors contributing to fatigue are relatively unclear. However, it has been suggested that fatigue is associated with dyspnea, anxiety, depression, and sleeping disorders.[230 233] Considering the complexity of the interaction among these three symptoms, using parallel questionnaires for their investigation could facilitate the future research to clarify and explore the relationship among pain, dyspnea, and fatigue.

Questionnaires with similar formats may better inform the relative severity and interference of these three symptoms in a particular patient. Pain has been widely investigated and several instruments have been developed to address its multidimensionality.[55] In addition, instruments that consist of multiple domains have been used to assess fatigue, such as

Multidimensional Fatigue Inventory,[234] the Manchester COPD-fatigue scale,[223] and Fatigue Impact Scale.[235] In contrast, the evaluation of dyspnea appears to lack a common, standardized instrument that encompasses several dimensions. Therefore, to date, available questionnaires do not allow comparable monitoring of pain, dyspnea, and fatigue because the nature and perspective of the questionnaire items vary markedly. As well, many of the questionnaires that evaluate one or two of these symptoms, such as the CRQ, are lengthy and require considerable time for scoring. Thus, using parallel questionnaires with a similar design could provide more practical and comparative assessment of these symptoms.

This study has some limitations. First, the participants of this study were recruited from the pulmonary rehabilitation programs, which may limit the generalizability of the results to patients with COPD outside of this sample. COPD patients with more complex comorbidities, frequent exacerbations and limited resources to attend rehabilitation may not be represented by this study group. Second, this study did not use pulmonary function measures to confirm COPD status between two administrations of the questionnaires. However, we issued a follow-up screening question to monitor changes in COPD status and all participants were well enough to attend rehabilitation sessions on both days of questionnaire completion. Finally, this study only used disease severity to determine the discriminant validity of the BFI and DI. Other indicators including physical performance and quality of life could be used in the future studies.

3.5 Conclusions

In conclusion, this study demonstrated good reliability and strong validity of the BFI and DI in patients with COPD. The BFI and DI are straightforward questionnaires for patients with

COPD to self-administer and require little time for the evaluator to score. Using these questionnaires, in conjunction with the BPI, may allow for efficient and concurrent assessment of common symptoms of COPD, providing comparative analyses to better inform clinical management and research investigations.

Chapter 4: Comorbidities that cause pain and the contributors to pain in patients with COPD

4.1 Introduction

COPD is a debilitating respiratory disease that is characterized by chronic airflow limitation.[40] However, COPD also has widespread systemic effects[40] and commonly coexists with more than one comorbidity, including CVD,[98] diabetes, [143] arthritis, [143] and osteoporosis.[66] It has been reported that 51% of patients with COPD have at least one comorbidity,[143] which is associated with increased mortality, hospitalization,[236] and poor quality of life.[101] Importantly, the presence of comorbidities in patients with COPD may contribute to pain,[66] an underappreciated feature of COPD.

The prevalence of pain in COPD is high, with reports ranging between 45% and 72%.[64 65] Of concern, pain in patients with COPD was shown to be associated with poor quality of life [49 50 65] and a lower physical activity level.[49 50] Moreover, patients with COPD with the most severe pain had a lower 6-minute walk distance and lower physical activity time (measured with accelerometry), compared with those with minimal or no pain.[50] Although studies to date have shown a high prevalence of pain associated with lower physical function and poor quality of life, its underlying contributors remain unclear.

Recently, investigators have described the association between comorbidities and pain in COPD.[53 66 105] The number of comorbidities was correlated to pain severity scores, measured by the BPI and MPQ,[49 66] and was also described as a risk factor for pain in this condition.[105] Compared with COPD patients without pain, those who experienced pain reported a higher

number of comorbidities.[105] Moreover, 73% of patients with COPD who experienced pain had more than two comorbidities; 46% of those who had pain reported more than three comorbidities.[66] Taken together, these data support the postulate that the presence of some comorbidities may be one of the contributors to pain in patients with COPD. Although a relationship between pain and comorbidities has been described, the most common comorbidity that causes pain in patients with COPD has not been identified. Also, no study has inquired about comorbidities that cause pain in COPD to date.

Clinically, pain can be a primary symptom of many disorders and the most common referral reason for seeking medical attention from a family physician.[237] In addition to the primary pathology, the perception of pain is complex and can be influenced by culture, sex,[57] and psychological factors.[238] Therefore, the purpose of this study was two-fold: (1) to determine comorbidities that cause pain; and (2) to determine the potential contributors to pain, including socioeconomic status, physical and psychological factors, and smoking history in COPD. Understanding comorbidities that cause pain and the related contributors to pain in COPD may provide clinicians insight into its causative factors and potential interventions.

4.2 Methods

4.2.1 Study protocol and participants

This was a cross-sectional survey study. It was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants of this study provided written informed consent.

A convenience sample of patients with COPD was recruited from pulmonary rehabilitation programs at six sites in Metro Vancouver and Okanagan regions of British Columbia, Canada from January 2014 to May 2015. All eligible participants who attended pulmonary rehabilitation programs at the participating centers were invited to participate in this study. Inclusion criteria were: (1) being aged > 40 years; and (2) having a diagnosis of COPD confirmed by spirometry. Exclusion criteria were: (1) lacking English fluency; or (2) having cognitive impairment that interfered with written consent and completion of questionnaires.

Participants were given a survey package that contained the following: (1) participant information form; (2) BPI[179]; (3) list of health conditions in lay terms that might contribute to pain; (4) medication record; (5) DI;[216] (6) BFI;[216] (7) Clinical COPD Questionnaire (CCQ);[239] and (8) the General Self-efficacy Scale (GSE).[240]

4.2.2 Outcome measures

4.2.2.1 Participant information form

This form asked for information on demographic characteristics, such as age, sex, height and weight. Socioeconomic status questions including education level, living status with family, employment status, work type, and housing situation were adapted from a previous study.[237]

4.2.2.2 Brief Pain Inventory

The BPI is a well-established pain questionnair[179] that consists of three components: (1) a body diagram to indicate pain locations; (2) a pain magnitude subscale, which consists of four items that ask about pain magnitude “now”, “worst level”, “least level”, and “on average”, respectively, via a numeric rating scale anchored by 0 (no pain) and 10 (pain as bad as you can imagine); and (3) a pain interference subscale, which contains seven items that evaluate how

pain interferes with seven daily life activities by using numeric rating scales anchored by 0 (does not interfere) and 10 (completely interferes).

4.2.2.3 List of health conditions that might contribute to pain and medication record

This form asks about comorbidities that cause pain stated in lay terms; for example, "Do you have pain and stiffness in your joints that hurt more when you walk or when you use the painful joints?". Two additional questions asked the presence of psychological comorbidities, depression and anxiety. This list was adapted from the Charlson comorbidity index,[241] our previous survey of pain in COPD,[49] and a recent survey about chronic pain.[242] Current medications were listed as well as the name, dose, frequency, and start date of medications. If affirmative responses were self-reported regarding comorbidities that cause pain, health professionals from the respective pulmonary rehabilitation program confirmed their presence by medical chart review or telephone call to the participant.

4.2.2.4 Dyspnea Inventory and Brief Fatigue Inventory

The DI and BFI[216] are questionnaires with a parallel format to the BPI that can evaluate dyspnea and fatigue, respectively. The magnitude and interference items are similarly devised compared to the BPI. The reliability and validity of the DI and BFI have been determined in patients with COPD.[243]

4.2.2.5 Clinical COPD Questionnaire

The CCQ is a validated disease-specific, health-related quality of life questionnaire[239] that is used to evaluate health status in patients with COPD. It consists of 10 items in three domains (symptoms, functional state, and mental state). A 7-point Likert scale from 0 to 6 is used for each item, with a lower score indicating a better outcome.

4.2.2.6 General self-efficacy scale

The GSE aims to assess the perceived self-efficacy, which is the extent of one's beliefs in his or her own ability to complete novel tasks and reach goals.[244] The GSE includes 10 items that ask how participants cope with different situations. Self-efficacy is assessed using a 4-point Likert scale from 1 to 4, with a higher score indicating higher self-efficacy.

4.2.3 Statistical analysis

A sample size of > 74 was calculated to provide an effect size (f^2) of 0.35, a power of 0.9 and an $\alpha_2 < 0.05$ for multiple linear regression analyses.[245]

Demographic data, the magnitude and interference scores of pain, dyspnea, and fatigue, as well as the CCQ and GSE scores, were summarized using descriptive statistics. Mean and standard deviations are reported. Frequencies were calculated for the prevalence of pain, and the number of comorbidities that cause pain.

Logistic regression models were built to determine factors associated with the presence of pain (binary outcome). The following potential independent variables were individually included in the models: age, sex, COPD severity (FEV_1), BMI, CCQ, GSE, socioeconomic status, smoking history, anxiety, and depression. A multiple logistical regression model was then performed to adjust potential confounders.

Linear regression models were used to determine the contributors of pain magnitude and interference scores by including the following potential independent variables: age, sex, COPD severity (FEV_1), BMI, CCQ, GSE, DI, BFI, socioeconomic status, smoking history, anxiety, and

depression. All statistical analyses were performed using SPSS (Version 22.0, Armonk, NY: IBM Corp) with a level of significance set at $p < 0.05$.

4.3 Results

In total, 100 of 137 (73%) participants returned the survey packages. Of those responders, four participants were excluded (three chose to withdraw from the study; one was a duplicate participant). As a result, 96 (70%) participants were included in this study. Demographics of participants are presented in Table 4.1.

Table 4.1 Demographic characteristics and outcome measures of participants

Characteristic	**Male (n = 57)**	**Female (n = 39)**	**Total (n = 96)**
Age (years)	71.9 (9.9)	70.1 (9.2)	71.2 (9.6)
FEV_1 (% predicted)	46.5 (19.0)*	58.3 (21.5)*	51.3 (20.8)
BMI (kg/m^2)	26.0 (0.1)	26.1 (6.9)	26.0 (6.4)
Smoking history (pack-year)	41.4 (28.1)	38.8 (22.7)	40.3 (25.8)
Current smoker; n (%)			
Yes	1 (1.7%)	3 (7.7%)	4 (4.2%)
No	51 (89.5%)	36 (92.3%)	87 (90.6%)
Unknown	5 (8.8%)	0 (0%)	5 (5.2%)
Highest completed education; n (%)			
High school	27 (47.3%)	21 (53.8%)	48 (50%)
College	13 (22.8%)	12 (30.8%)	25 (26%)

Characteristic	Male (n = 57)	Female (n = 39)	Total (n = 96)
Bachelor	8 (14%)	2 (5.1%)	10 (10.4%)
Master or doctorate	3 (5.3%)	1 (2.6%)	4 (4.2%)
Professional degree	3 (5.3%)	2 (5.1%)	5 (5.2%)
Unknown	3 (5.3%)	1 (2.6%)	4 (4.2%)
Living status at home; n (%)			
Live with family members that need support	12 (21.1%)	1 (2.6%)	13 (13.5%)
Live with family members that can provide support	21 (36.8%)	9 (23.1%)	30 (31.3%)
Live alone	7 (12.3%)	20 (51.2%)	27 (28.1%)
Other	4 (7%)	0 (0%)	4 (4.2%)
Unknown	13 (22.8%)	9 (23.1%)	22 (22.9%)
Work status; n (%)			
Paid work	3 (5.3%)	5 (12.8%)	8 (8.3%)
Unpaid work	2 (3.5%)	0 (0%)	2 (2.1%)
Unable to work	13 (22.8%)	5 (12.8%)	18 (18.8%)
Retired	39 (68.4%)	28 (71.8%)	67 (69.8%)
Unknown	0 (0%)	1 (2.6%)	1 (1%)
Type of work; n (%)			
Sitting most of the day	2 (3.5%)	2 (5.1%)	4 (4.2%)
Light activity	0 (0%)	3 (7.7%)	3 (3.1%)
Moderate labor	2 (3.5%)	1 (2.6%)	3 (3.1%)

Characteristic	Male (n = 57)	Female (n = 39)	Total (n = 96)
Heavy labor	1 (1.7%)	0 (0%)	1 (1%)
Unable to work	10 (17.6%)	5 (12.8%)	15 (15.6%)
Retired	36 (63.2%)	25 (64.1%)	61 (63.6%)
Unknown	6 (10.5%)	3 (7.7%)	9 (9.4%)
Housing situation; n (%)			
Rent	22 (38.6%)	15 (38.5%)	37 (38.6%)
Own	34 (59.7%)	22 (56.4%)	56 (58.3%)
Unknown	1 (1.7%)	2 (5.1%)	3 (3.1%)
Pain†			
Pain magnitude score	4.1 (1.9)	3.9 (1.5)	4.0 (1.7)
Pain interference score	3.9 (2.2)	3.4 (2.1)	3.7 (2.1)
Dyspnea†			
Dyspnea magnitude score	4.8 (1.9)	4.6 (2.0)	4.7 (1.9)
Dyspnea interference score	4.4 (2.1)	3.6 (2.2)	4.1 (2.1)
Fatigue†			
Fatigue magnitude score	5.1 (1.7)	4.9 (1.9)	5.0 (1.8)
Fatigue interference score	4.2 (2.3)	3.8 (2.1)	4.0 (2.2)
CCQ score	3.0 (1.0)*	2.5 (1.0)*	2.8 (1.0)
GSE score	3.1 (0.4)	3.1 (0.5)	3.1 (0.5)

Data are presented as mean (SD) or n (%)

* *p*-value < 0.05

† Calculated in people who reported symptoms

4.3.1 The prevalence and characteristics of pain

Sixty-eight of 96 (71%) participants with COPD reported pain on the BPI. A total of 156 pain locations were identified (Figure 4.1) with low back being the most common pain location (41.2%), followed by the knee (25%) and shoulder (23.5%). Of five body regions (head and face, neck, trunk, upper extremity, and lower extremity), pain was most often reported in the trunk (57%) followed by the lower extremity (38%). The average pain magnitude and interference scores were 4.0 ± 1.7 and 3.7 ± 2.1 out of 10, respectively. Of the 68 participants who reported chronic or recurrent pain that lasted > 3 months, 51 participants (75%) had been seeking treatments for pain during the last week, including prescribed or over-the-counter medications (n = 46; 90.2%), physical therapy (n = 6; 11.8%), complementary therapy (n = 1, 1.9%), psychological therapy (n = 1; 1.9%), and other types of therapy (n = 2; 3.9%).

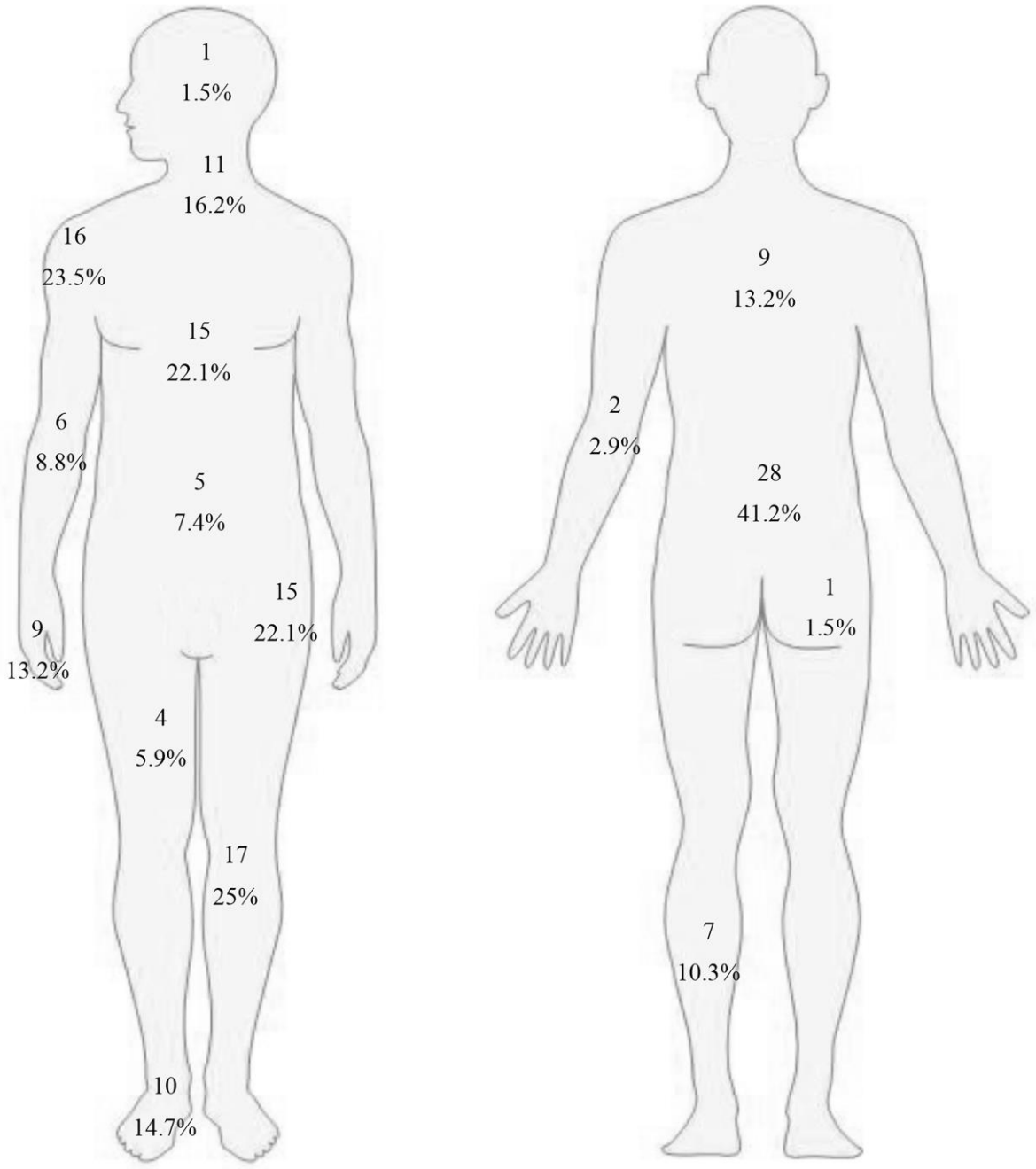

Figure 4.1 Pain location reported by 68 participants with COPD

Modified with permission from Motifolio Inc.

4.3.2 Comorbidities that caused pain

In the 68 participants who had pain, 293 comorbidities that caused pain were reported (Table 4.2). On average, each participant experienced 4.3 ± 2.6 comorbidities that caused pain. Most (59 of the 68 participants) reported more than one comorbidity that caused pain (Figure 4.2). The most common comorbidities that caused pain were arthritis (75%), followed by back problems (47.1%) and muscle cramps (45.6%). Moreover, depression and anxiety were self-reported in 44.1% and 11.8% of participants, respectively.

Table 4.2 Prevalence of comorbidities that cause pain and psychological comorbidity (n = 68)

Comorbidity type	Prevalence
Comorbidities that cause pain	n (%)
Pain and stiffness in joints due to arthritis	51 (75%)
Back problem that causes pain	32 (47.1%)
Muscle cramp	31 (45.6%)
Neck problem that causes pain	23 (33.8%)
Heartburn/ acid reflux	23 (33.8%)
Fractures/ joint replacement	22 (32.4%)
Nerves problem that causes pain	18 (26.5%)
Compression fractures due to osteoporosis	15 (22.1%)
Chest pain due to heart condition	10 (14.7%)
Calf pain due to blood vessel disease	10 (14.7%)
Chronic fatigue syndrome/ fibromyalgia	10 (14.7%)
Headaches/ migraines	9 (13.2%)
Cancer	8 (11.8%)
Neuropathy due to diabetes	6 (8.8%)
Pain in head or face	5 (7.4%)
Other health problems that cause pain	20 (29.4%)
Psychological comorbidity	n (%)
Depression	30 (44.1%)
Anxiety	8 (11.8%)

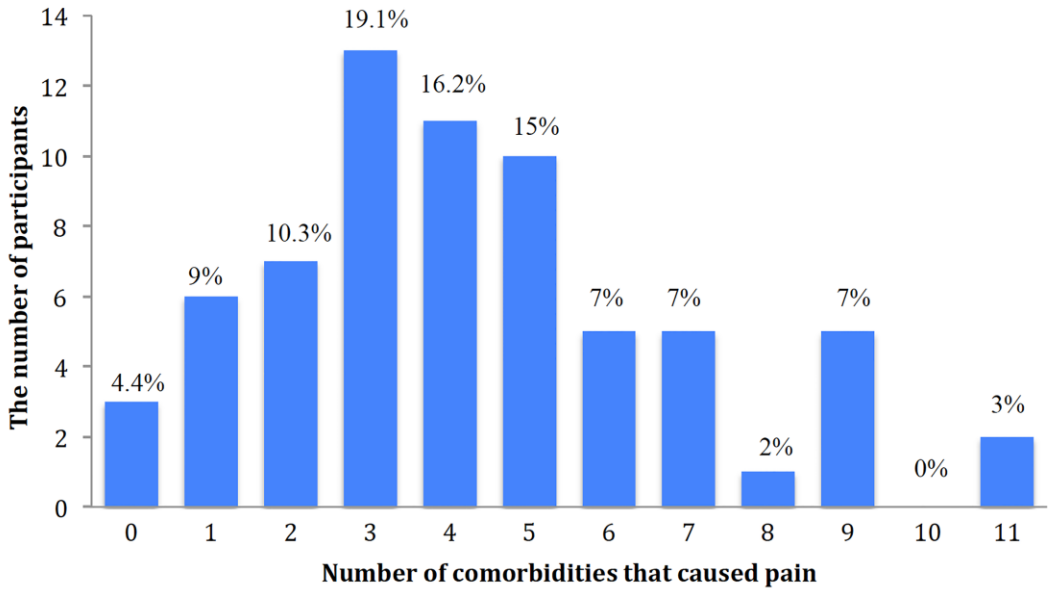

Figure 4.2 Distribution of the number of comorbidities that caused pain in individuals with COPD who reported pain (n = 68)

4.3.3 Factor associated with pain in people with COPD

Table 4.3 presents the relationship between pain and each potential independent variable. A lower self-efficacy (GSE) score (OR = 0.19, 95% CI = 0.06 − 0.64), and renting rather than owning home (OR = 0.24, 95% CI= 0.08 − 0.71) were individually associated with pain in individuals with COPD. The final model adjusted by multiple covariates is shown in Table 4.4 (χ^2 = 10.42, p = 0.005). A higher GSE score was associated with decreased likelihood of pain (OR = 0.25, 95% CI = 0.06 − 0.94), while adjusting for the housing situation. Home owners compared with renters were less likely to have pain (OR = 0.28, 95% CI = 0.08 − 0.96), while controlling for GSE scores.

Table 4.3 Unadjusted OR of potential independent variables associated with the presence of pain (n = 96)

Variable	Unadjusted OR (95% CI)
Age	0.98 (0.93, 1.03)
Sex	
Female	1.00
Male	0.75 (0.30, 1.86)
BMI (kg/m^2)	1.00 (0.93, 1.07)
CCQ scores	1.26 (0.79, 2.01)
GSE scores	0.19 (0.06, 0.64)*
FEV_1 (% predicted)	1.01 (0.99, 1.03)
Smoking history (pack-year)	1.00 (0.98, 1.03)
Education	
High school	1.00
College	1.82 (0.57, 5.77)
Bachelor	1.82 (0.34, 9.61)
Master or doctorate	1.36 (0.13, 14.21)
Professional degree	0.68 (0.10, 4.52)
Housing situation	
Rent	1.00
Own	0.24 (0.08, 0.71)*
Anxiety	
No	1.00
Yes	1.40 (0.28, 7.13)
Depression	
No	1.00
Yes	2.84 (0.95, 8.54)

*p-value < 0.05

Abbreviations: BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume in one second; OR = odds ratio

Table 4.4 Factors associated with the presence of pain adjusting by the multiple covariates

Variable	Adjusted OR (95% CI)
GSE scores	0.25 (0.06, 0.94)*
Housing situation	
Rent	1.00
Own	0.28 (0.08, 0.96)*

*p-value < 0.05

Abbreviations: CI = confidence interval; OR = odds ratio

4.3.4 Contributors to pain magnitude and pain interference scores

The BFI total score was the only significant contributor to the BPI magnitude score. There was a significant association between the BPI magnitude score and the BFI total score ($F_{1,64}$= 13.9, $p < 0.001$), with an R^2 of 0.18. It was found that the BPI magnitude score increases by 0.35 on average in participants when their total BFI score increases one point (regression coefficient = 0.35, standard error = 0.09).

The BPI magnitude score and the BFI total score were significantly associated with the BPI interference score ($F_{2,63}$ = 41.5, $p < 0.001$), with an R^2 of 0.57. The adjusted regression coefficients of the contributors are presented in Table 4.5. Both the BPI magnitude score and the BFI total score were significant contributors to the BPI interference score.

Table 4.5 Adjusted regression coefficients of the contributors to the BPI interference score

Variable	Adjusted regression coefficient (95% CI)	Standard error
BPI magnitude score	0.53 (0.30, 0.76)*	0.11
BFI total score	0.48 (0.29, 0.67)*	0.09

*p-value < 0.05

Abbreviations: BPI = Brief Pain Inventory; BFI = Brief Fatigue Inventory

4.4 Discussion

This study is the first to describe the underlying contributors to pain in patients with COPD who attend pulmonary rehabilitation programs. In this study, 71% of participants with COPD experienced significant pain and the most common comorbidities that cause pain were arthritis, followed by back problems, and muscle cramps. Patients with COPD who had a lower self-efficacy, and who rented rather than owned their home were more likely to have pain. Lastly, both pain severity and total BFI scores were contributors to pain interference with daily aspects of living.

The prevalence of pain in participants with any stage of COPD in this current study (71%) compared favorably to that in one report[65] (72%), a hospital outpatient cohort, but was higher than the prevalence found in a study[64] that recruited participants from a pulmonary rehabilitation program (45%). Although all three studies utilized self-reported questionnaires to determine the presence of pain, different instruments and definitions of pain prevalence may have contributed, at least in part, to the variability in these data. Both this current study and a previous study[65] that used the BPI showed a similar pain prevalence. In contrast, the study[64] that showed a lower pain

prevalence used 0 to 10 numeric rating scales and defined the presence of pain as a score larger than 0. Also, the two previous studies were conducted in Norway,[64 65] whereas this study recruited participants in Canada. Perceptual experience of pain can be affected by cultural factors.[57] However, to date, no single study has investigated the prevalence of pain using a uniform methodology among patients with COPD across multiple countries. Thus, the prevalence of pain in patients with COPD may vary across studies that were conducted in different countries using different methodologies.

The prevalence of pain in the general population ranges from 24.4% to 50.4% in population-based studies.[63 107 246] The direct comparison of the pain prevalence and severity among this current study and previous studies was not meaningful because of the variance of the participants enrolled and the instruments used to measure pain. However, a few studies have confirmed that the pattern of pain differs between patients with and without COPD after controlling for confounders. Compared with the age- and sex-matched general population, the prevalence of pain was significantly higher in patients with COPD.[49 63] Similarly, patients with COPD had a higher pain prevalence than those who live with other chronic conditions.[70] Also, patients with COPD reported significantly higher pain magnitude and interference scores measured by the BPI than those without COPD, after controlling for age and sex.[49] The different pain patterns between individuals with and without COPD may be caused by the presence of comorbidities[105] and alterations of pain thresholds in COPD.[94 247]

Arthritis and back problems were the most frequent comorbidities that caused pain, which is consistent with the trunk region (shoulder, chest, abdomen, back, hip, and buttock) being the most commonly reported location of pain in this study, followed by the lower

extremity. These data are consistent with the regions where pain was most often reported in COPD.[54 65 66 68] Musculoskeletal disease is a common comorbidity of COPD[66 143] and accounts for 26% of chronic pain in the general population.[106] Previous research[50 105 143] has confirmed that two common age-related musculoskeletal diseases, osteoporosis and osteoarthritis, are highly prevalent comorbidities in COPD. Studies have shown that the risk of osteoporosis in patients with COPD is higher than that in healthy, age-matched individuals.[248] Factors that may contribute to a high prevalence of osteoporosis among patients with COPD include smoking,[249] limited physical activity,[250] the use of corticosteroids,[251] and hypercapnia or hypoxia resulting from airflow obstruction.[252] The primary cause of pain in osteoporosis is due to fracture, especially vertebral fractures.[253] On the other hand, osteoarthritis, the most common type of arthritis, is a prevalent degenerative joint condition among older adults, particularly in the knee and hip joints.[254] Because COPD is more common with increasing age,[40] it might be expected that osteoarthritis frequently coexists with COPD. Since the hallmark symptom of osteoporosis and osteoarthritis is pain, it is not surprising that the results demonstrated the most frequently reported pain locations were the low back and knees.

Even though CVD is one of the most common comorbidities of COPD,[66 98 143] this study found that the prevalences of chest pain caused by a heart condition and calf pain caused by a blood vessel disease were much lower than other causes. Increasing age and more severe COPD are associated with a higher risk of CVD,[144] and the presence of CVD frequently contributes to hospitalization among patients with COPD,[98] who may not be able to participate in a pulmonary rehabilitation program. Also, pulmonary rehabilitation programs improve cardiovascular risk factors and function.[255] The moderate COPD severity (FEV_1 = 51.3% predicted) of the

participants in this study and their participation in a pulmonary rehabilitation program may be two factors that explain why CVD was not a frequent cause of pain. In addition, 30% to 60% of patients with CVD do not experience pain.[141] Taken together, although CVD is common in COPD, it likely is not a primary cause of pain in this chronic lung disease.

When considered independently, self-efficacy and housing situation were two factors that increased the risk of pain in patients with COPD. Self-efficacy, defined as a personal belief that one has the ability to perform certain behaviors successfully,[244] has been shown to be associated with pain tolerance[256] and pain perception.[257] People with higher self-efficacy may show better pain control and perform better on physical challenges.[257] On the other hand, the prevalence of pain is associated with lower socioeconomic status.[258] Considering that self-efficacy is related to socioeconomic status,[259] socioeconomic status is a potential confounder of the relationship between the presence of pain and self-efficacy, and vice versa. Therefore, to adjust for potential confounders, multiple logistic regression models were used. Self-efficacy and housing situation were not significant contributors to pain interference with daily aspects of living. Instead, the contributors to pain interference included pain magnitude and total fatigue scores. An explanation of the discrepancy between analyses might be due to the fact that only participants who reported pain provided their pain magnitude and interference scores. For those who did not experience pain, their self-efficacy scores were significantly higher ($p < 0.01$) but were not captured in the regression analysis. Also, the self-efficacy questionnaire uses a 4-point Likert scale from 1 to 4, which might limit the discrimination of different levels of self-efficacy.[260] The contribution of pain magnitude and total fatigue scores contributing to pain interference in patients with COPD is similar to findings in other chronic conditions. Previous studies have

found that pain is associated with fatigue in cancer[261] and rheumatoid arthritis.[262] Also, pain can interfere with sleep and contribute to poor sleep quality that could aggravate the level of fatigue.[261]

This study is limited to some extent by the survey methodology of self-reporting by participants. However, because pain, fatigue, dyspnea, QOL, and self-efficacy are subjective, self-report questionnaires can be the most accurate measures. Second, the questionnaire that queried comorbidities that caused pain sometimes listed symptoms (e.g. muscle cramp, heartburn) rather than the disease. To verify these responses, the participant's self-report was confirmed by health professionals from the participant's pulmonary rehabilitation program. Nonetheless, one-on-one interviews and physical exams may provide more in-depth and varied causes of pain in patients with COPD compared with the survey methodology used in this study. Third, multiple-choice options about socioeconomic indicators may not provide important contextual issues. Also, Metro Vancouver is one of the most expensive cities in Canada. Housing situation may not present the socioeconomic status precisely, although housing situation can be considered as one of the indices of socioeconomic status.[237] Future studies that ask more specific questions about socioeconomic status are required. Lastly, the participants of this study were recruited from pulmonary rehabilitation programs in the most western province of Canada, which might limit the generalizability of the findings to other regions or to patients with COPD who have not participated in pulmonary rehabilitation programs.

4.5 Conclusions

In conclusion, pain is very common in COPD and is primarily associated with musculoskeletal conditions and muscle cramps. The severities of pain and fatigue are primary contributors to how pain interferes with daily aspects of living. Many of the items of the pain interference scale are descriptors fundamental to health such as sleep and physical activity. Pain, together with more commonly reported symptoms of dyspnea and fatigue, might severely limit exercise and physical activity in patients with COPD and contribute to poor QOL. Given that physical activity is the best predictor of all-cause mortality in COPD[263] and is widely promoted in several clinical guidelines,[40 264] mitigating barriers is of utmost importance. Pain assessment and management should be essential components of management for patients with COPD to improve QOL and physical activity.

Chapter 5: A comparison of pain, fatigue, dyspnea and their impact on quality of life in pulmonary rehabilitation participants with COPD

5.1 Introduction

Dyspnea and fatigue are primary symptoms of COPD with the reported prevalence values ranging from 60% to 93%[265-267] and 50% to 95%,[266 268] respectively. These symptoms not only limit exercise capacity[48] and physical activity,[268 269] but also impact quality of life[47 212] and contribute to higher hospitalization rates and mortality in patients with COPD.[36] Recently, it has been demonstrated that pain is very prevalent in patients with COPD and they experienced more pain compared to age- and sex-matched general cohorts.[49 63] The reported prevalence ranges between 45% and 72%.[54 63 65] Similar to dyspnea and fatigue, pain in COPD is associated with impaired quality of life and physical activity levels.[49 50 65] Considering the high prevalence of these three symptoms, determining their relative contributions to limiting aspects of daily living and quality of life may facilitate improved management of COPD.

The etiology of pain in COPD is likely multifactorial and has been postulated to arise from pulmonary and extrapulmonary pathophysiology, some of which might be shared with dyspnea and fatigue. Patients with COPD have reported pain to be most commonly due to musculoskeletal conditions[66 105 270] and it has been associated with vertebral deformities.[271] In contrast, dyspnea and fatigue have been primarily attributed to pathologic changes of the lung associated with COPD[47 272] that can result in secondary manifestations with the primary one being a lack of cardiovascular fitness.[273] The interrelationships among dyspnea, fatigue, and pain may be due to activation of similar networks in areas of the brain.[231 274] The repetitive experience

of these symptoms can cause permanent changes that influence perception and alter the ability to differentiate between noxious stimuli.[275] Association between fatigue and dyspnea has been reported in patients with COPD.[230 276] More linkages between pain and dyspnea[277] or fatigue[278] are described in healthy individuals and persons with lung cancer, respectively. Given their common processing brain locales and evidence of associations between different pairs of these three symptoms, it is possible that pain may be associated with dyspnea and/ or fatigue in patients with COPD.

Due to the perceptual nature of dyspnea, fatigue, and pain, they are frequently quantified by self-reported questionnaires. To date, no study has used parallel formats to evaluate the magnitude and respective interference of these three symptoms with one exception. A Japanese study utilized the BPI, BFI, and DI[216] to quantify symptom severity and how each symptom interferes with aspects of daily living in lung cancer patients.[179] Because the BPI, BFI, and DI utilize similar items that are quantified with identical numeric scales, the magnitude and how each symptom limits aspects of daily living can be readily compared.

To our knowledge, there is no study has concurrently examined dyspnea, fatigue, and pain in patients with COPD using similarly formatted questionnaires. Although the impact of dyspnea, fatigue, and pain on quality of life has been examined in patients with COPD,[47 65 212] no investigation has concurrently reported their impact in the same group of patients. Furthermore, none of these studies has considered the interactions of these symptoms. Therefore, the purpose of this study was to: (1) compare the prevalence and magnitude of dyspnea, fatigue, and pain in COPD patients and how each symptom limits aspects of daily living; (2) determine association between pain and the other two symptoms; (3) assess the impact of these three symptoms on

quality of life in patients with COPD. We hypothesized that: (1) the magnitude and interference scores of the three symptoms would not differ significantly; (2) pain would be associated with dyspnea and fatigue; (3) all three symptoms would negatively impact on quality of life after controlling for confounders.

5.2 Methods

5.2.1 Designs and participants

This was a cross-sectional study that utilized a survey method. This study was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants of this study provided written informed consent.

Participants were recruited from pulmonary rehabilitation programs at six sites in the large (2.4 million) and small cities (40,000) of British Columbia, Canada, from January 2014 to May 2015. Patients with COPD are referred to a pulmonary rehabilitation program by respirologists if they have: (1) COPD diagnosed by spirometry; (2) persistent symptoms and limited in daily life activities despite optimal pharmacotherapy; (3) no medical condition that precludes them from participating in an exercise program; and for most programs (4) have quit smoking or are in the process of quitting.

The inclusion criteria were people who were over 40 years of age with a respirologists-diagnosed COPD based on spirometry. People were excluded if they lacked English written fluency or had cognitive impairment that interfered with informed consent or the ability to complete questionnaires provided in English.

Participants were asked to complete the following questionnaires: (1) BPI; (2) DI; (3) BFI; and (4) CCQ. Demographic characteristics including post-bronchodilator FEV_1, age, and sex were collected by the rehabilitation practitioners working in the respective rehabilitation programs. All data were provided to the investigators in a de-identified manner.

5.2.2 Outcome measures

5.2.2.1 Brief Pain Inventory

The BPI is a commonly used pain questionnaire with good reliability and validity.[179] It has three components: (1) a body diagram that is used to indicate pain locations. Participants are asked to shade the areas where they feel pain and place an "X" on the area that hurts the most; (2) a magnitude domain consisting of four items that ask about pain magnitude "now", "worst level", "least level", and "on average" respectively. Each item is rated using a numeric rating scale anchored by 0 (no pain) to 10 (pain as bad as you can imagine); (3) an interference domain that contains seven items querying how pain interferes with seven aspects of daily living. Each item is rated using a numeric rating scale anchored by 0 (does not interfere) to 10 (completely interferes).

5.2.2.2 Dyspnea Inventory and Brief Fatigue Inventory

The DI and BFI[216] are questionnaires with parallel formats to the BPI that evaluate dyspnea and fatigue, respectively. The first three items of both questionnaires query about symptom magnitude "now", "usual level" and "worst level" via numeric rating scales anchored by 0 (no dyspnea/fatigue) to 10 (as bad as you can imagine). Symptom interference with daily life activity is evaluated by seven (the DI) and six (the BFI) items with numeric rating scales

anchored by 0 (doesn't interfere) to 10 (completely interferes). The DI and BFI have been validated in individuals with COPD.[243]

5.2.2.3 Clinical COPD Questionnaire

The CCQ is a validated health-related quality of life questionnaire for individuals with COPD.[239] It consists of 10 items in three domains (symptoms, functional state, and mental state). A 7-point Likert scale from 0 to 6 is used for each item with lower scores indicating better outcomes.

5.2.3 Statistical analysis

Demographic data, the CCQ scores, and the magnitude and interference scores of pain, dyspnea, and fatigue were analyzed using descriptive statistics. Means and standard deviations were reported for these outcomes and frequencies were calculated for the prevalence of each symptom. One way within-subjects ANOVA tests were performed to compare pain, fatigue, and dyspnea. The correlations among dyspnea, fatigue, and pain were examined using Spearman rank correlations. Simple linear regression analyses were first performed to determine the association between each symptom and quality of life. Hierarchical multiple linear regression analyses were then used to determine the impact of the symptoms on quality of life. In stage 1, the following potential confounders were entered in the regression model: age, sex, and disease severity based on FEV_1 % predicted values. All three symptom variables (dyspnea, fatigue, and pain) were then entered in stage 2. Statistical analyses were performed using SPSS (Version 22.0, Armonk, NY:IBM Corp). A p-value < 0.05 was set to indicate significant differences.

5.3 Results

5.3.1 Flow of participants through the study

A sample size of > 74 was calculated to provide an effect size (f^2) of 0.35, a power of 0.9, and an $\alpha_2 < 0.05$ for multiple linear regression analyses.[245] In total, 91 participants returned the completed questionnaires. The demographic characteristics of participants are presented in Table 5.1.

Table 5.1 Demographic characteristics and outcome measures of participants (n = 91)

	Mean (SD)	**Range**
Age (years)	70.7 (9.5)	49 − 88
Sex n (%)		
Male	52 (57%)	
Female	39 (43%)	
BMI (kg/m^2)	25.9 (6.1)	16.2 − 48.7
FEV_1 (% predicted)	51.1 (21.2)	14 − 119
COPD severity[†]		
Mild	10 (11%)	
Moderate	32 (35%)	
Severe	34 (37%)	
Very severe	13 (14%)	
Smoking history (pack-year)	41.5 (25.9)	3.6 − 104
CCQ score		
Symptom domain	2.8 (1.1)	0.3 − 5.5
Functional state domain	2.9 (1.1)	0 − 6.0
Mental state domain	2.6 (1.6)	0 − 6.0
Total score	2.8 (1.0)	0.4 − 5.0

[†] COPD severity of two participants were missing

Disease severity was classified using GOLD criteria[1]

Abbreviations: BMI = body mass index; CCQ = Clinical COPD Questionnaire; FEV_1 = forced expiratory volume in one second; n = sample size

5.3.2 A comparison of dyspnea, fatigue, and pain

Prevalence of the three symptoms was more than 70%, with dyspnea having the highest prevalence followed by fatigue and pain (prevalence of 93%, 77%, and 74%, respectively). There was no statistically significant difference in demographic characteristics among those who reported dyspnea (n = 85), fatigue (n = 70), and pain (n = 67) ($p > 0.05$). Worthy of note, all three symptoms demonstrated a magnitude domain score between 4.5 and 5.0 on a 10-point numeric scale (Table 5.2).

Table 5.2 The demographics and prevalence and mean scores of dyspnea, fatigue, and pain (n = 91)

	Dyspnea	Fatigue	Pain
Prevalence; n (%)	85 (93%)	70 (77%)	67 (74%)
Demographic characteristics			
Age (years)	70.4 (9.7)	70.7 (9.5)	70.4 (9.7)
FEV_1 (% predicted)	50.7 (21.7)	52.3 (21.9)	52.5 (22.7)
Smoking history (pack-year)	42.1 (26.4)	44.6 (26.6)	42.2 (25.2)
BMI (kg/m^2)	25.9 (6.3)	25.9 (6.1)	26.0 (6.14)
Magnitude domain			
Worst level	6.8 (2.3)	6.6 (2.1)	5.9 (1.7)
Average/ Usual level	4.1 (2.2)	4.4 (1.8)	4.0 (2.0)
Right now	3.3 (2.5)	4.0 (2.3)	3.5 (2.3)
Magnitude domain score	4.7 (1.9)	5.0 (1.8)	4.5 (1.7)
Interference domain			
Interfered with general activity	4.9 (2.8)	4.4 (2.5)	4.0 (2.5)
Interfered with mood	3.0 (2.6)	2.7 (2.5)	3.3 (2.7)
Interfered with walking ability	5.4 (2.9)	4.9 (2.8)	4.2 (3.0)
Interfered with normal work	5.3 (2.7)	5.0 (2.6)	4.5 (2.6)
Interfered with relations with others	2.8 (2.6)	2.8 (2.6)	2.2 (2.5)
Interfered with sleep	2.6 (2.6)	--	3.7 (2.7)
Interfered with enjoyment of life	4.6 (2.9)	4.4 (2.9)	4.1 (2.6)
Interference domain score	4.1 (2.1)	4.0 (2.2)	3.7 (2.1)
Total score	4.3 (2.0)	4.3 (2.0)	3.9 (1.9)

*Data are presented as mean (SD) and calculated in people who reported symptoms

Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume in one second

A further analysis of dyspnea, fatigue, and pain within subjects was examined in participants who reported the presence of all three symptoms. An *a priori* sample size calculation was performed and a sample size of > 35 was calculated to provide a medium effect size (*f*) of 0.25, a power of 0.9, and an $\alpha_2 < 0.05$ for within-subjects ANOVA tests.[245] There were 48 participants who reported the presence of all three symptoms being included in the analyses. The magnitude worst level and magnitude subtotal scores differed significantly among three symptoms ($F_{2,92} = 6.8$, $p < 0.01$ and $F_{2,92} = 3.3$, $p < 0.05$, respectively). Dyspnea and fatigue were significantly higher than pain in the "worst level" item scores (Figure 5.1a); fatigue was significantly higher than pain in the magnitude domain scores (Figure 5.1d). The item scores of general activity and mood were significantly different among the three symptoms in the interference domain ($F_{1.7,79.9} = 3.1$, $p < 0.05$ and $F_{1.8, 82.7} = 3.6$, $p < 0.05$, respectively). Dyspnea score was significantly higher than pain in general activity (Figure 5.1e) whereas pain and dyspnea scores were significantly higher than fatigue in mood (Figure 5.1f). Pain score was also significantly higher than dyspnea in sleep ($F_{1,46} = 7.4$, $p < 0.01$) (Figure 5.1j). There was no significant difference reported among the three symptoms for total scores (Figure 5.1m).

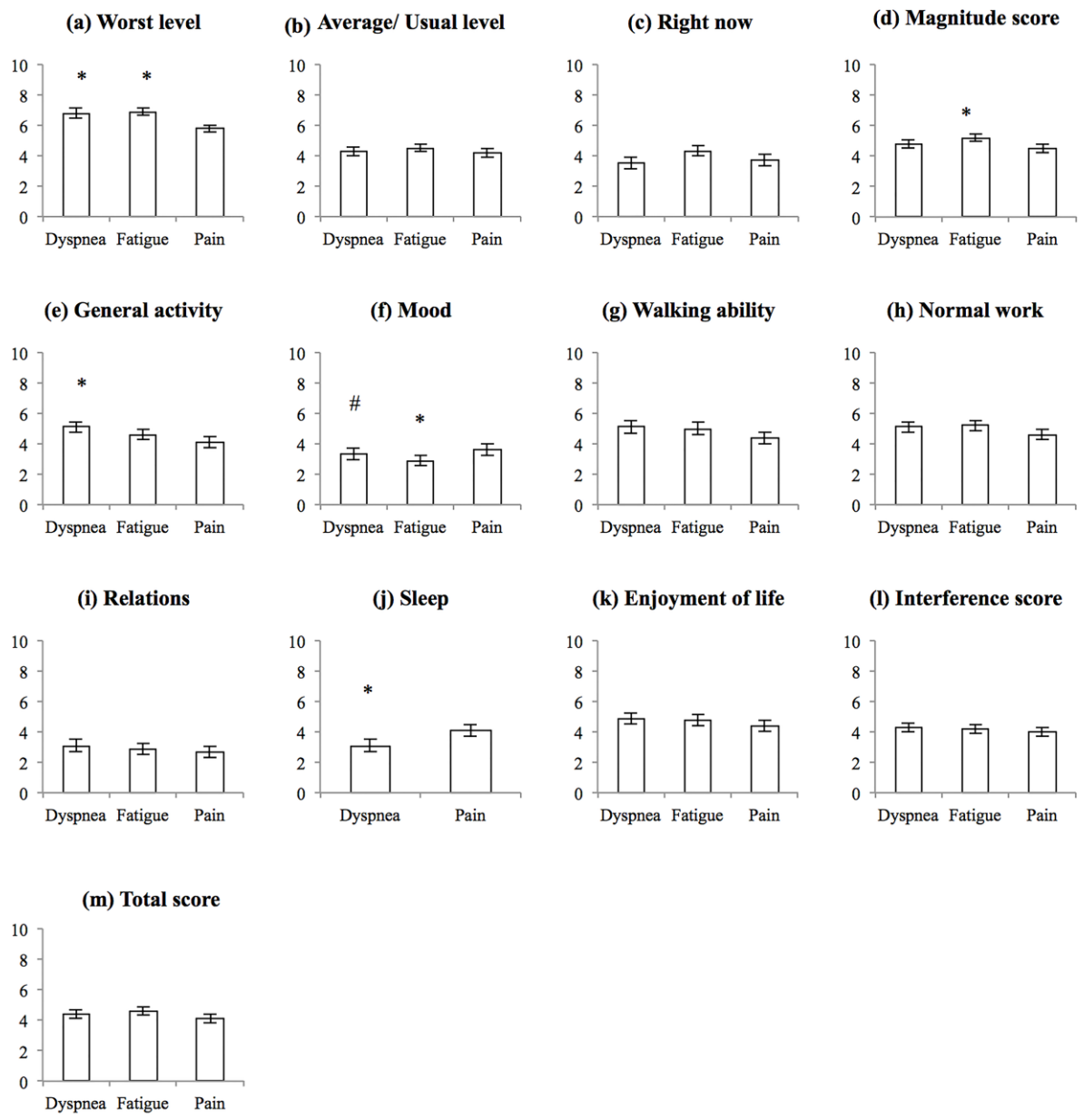

Figure 5.1 Bar plots showing the mean scores of the dyspnea, fatigue, and pain in the magnitude and interference domain within subjects who reported all the three symptoms (n = 48)

* *p*-value < 0.05 when compared with pain; # *p*-value < 0.05 when compared with fatigue

Error bars represent one standard error

5.3.3 Relationships among dyspnea, fatigue, and pain

The three symptoms were moderately-to-highly correlated with each other. The total DI scores were positively correlated with the total BFI scores ($\rho = 0.78$, $p < 0.01$) and the total BPI scores ($\rho = 0.49$, $p < 0.01$), and the total BPI scores were positively correlated with the total BFI scores ($\rho = 0.58$, $p < 0.01$). Modest negative correlations were shown between dyspnea and age, as well as fatigue and age. Pain was the only symptom that was not associated with age and/or FEV_1 (Table 5.3).

Table 5.3 The relationships among symptoms, age, and disease severity

	Dyspnea	**Fatigue**	**Pain**
Dyspnea†	--		
Fatigue†	0.78 (0.57, 0.99)**	--	
Pain†	0.49 (0.25, 0.74)**	0.58 (0.33, 0.82)**	--
Age	-0.27 (-0.48, -0.06)*	-0.23 (-0.44, -0.01)*	-0.07 (-0.32, 0.17)
FEV_1	-0.21 (-0.43, 0.01)	-0.19 (-0.4, 0.03)	0.07 (-0.18, 0.32)

Data are presented as spearmen correlation coefficient ρ (95% CI); n = 91

† The total scores from the DI, BFI, and BPI were used

*p-value < 0.05; **p-value < 0.01.

Abbreviation: FEV_1 = forced expiratory volume in one second

5.3.4 Impacts of symptoms on quality of life

The total DI, BFI, and BPI scores were individually associated with the symptom domain, functional state domain, mental state domain, and total scores of the CCQ (Table 5.4). In order to better understand the effect size of the symptoms on quality of life, 2-stage hierarchical multiple regression analyses were performed. Demographic variables were entered in the first stage and age was associated with the CCQ total scores ($F_{3,61} = 3.98$, $p < 0.05$). Age accounted for 12% of the variance in the CCQ total scores. When entering the total scores of three symptoms in stage 2, the results showed that dyspnea and fatigue were significant contributors to the CCQ total scores ($F_{6,58} = 27.24$, $p < 0.001$). Dyspnea and fatigue explained 71% of the variance in the CCQ total scores. Also, dyspnea was the only symptom associated with every domain of the CCQ after controlling for the confounders. Table 5.5 presents the adjusted regression coefficients of the variables in the models.

Table 5.4 Unadjusted regression coefficient of potential independent variables associated with quality of life (n = 91)

	Dependent variable-CCQ											
	Symptom domain			Functional state domain			Mental state domain			Total score		
	B (95% CI)	SE	β	B (95% CI)	SE	β	B (95% CI)	SE	β	B (95% CI)	SE	β
Dyspnea†	0.32 (0.23, 0.42)*	0.05	0.58*	0.39 (0.31, 0.47)*	0.04	0.72*	0.59 (0.48, 0.70)*	0.06	0.74*	0.40 (0.34, 0.47)*	0.03	0.81*
Fatigue†	0.29 (0.19, 0.38)*	0.05	0.55*	0.38 (0.30, 0.46)*	0.04	0.72*	0.51 (0.38, 0.63)*	0.06	0.66*	0.37 (0.30, 0.43)*	0.03	0.77*
Pain†	0.25 (0.10, 0.40)*	0.07	0.38*	0.27 (0.13, 0.41)*	0.07	0.42*	0.40 (0.21, 0.60)*	0.10	0.45*	0.29 (0.16, 0.41)*	0.06	0.49*
Age	-0.03 (-0.06, -0.01)*	0.01	-0.27*	-0.02 (-0.05, 0.004)	0.01	-0.18	-0.03 (-0.07, 0.004)	0.02	-0.18	-0.03 (-0.05, -0.006)*	0.01	-0.26*
Sex- male	0.50 (0.02, 0.98)*	0.24	0.22*	0.49 (0.02, 0.97)*	0.24	0.22*	0.31 (-0.39, 1.01)	0.35	0.09	0.46 (0.03, 0.89)*	0.22	0.22*
FEV_1	-0.007 (-0.02, 0.004)	0.006	-0.13	-0.02 (-0.03, -0.007)*	0.005	-0.34*	-0.01 (-0.03, 0.005)	0.008	-0.15	-0.01 (-0.02, -0.002)*	0.005	-0.25*

*p-value < 0.05

† The total scores from the DI, BFI, and BPI were used

Abbreviations: CCQ = Clinical COPD Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in one second; B = unstandardized regression coefficient (unadjusted); SE = standard error; β = standardized regression coefficient (unadjusted)

Table 5.5 Two-stage hierarchical multiple regression analysis results of the CCQ scores by the symptoms (n = 91)

	Dependent variable-CCQ			
	Symptom domain	**Functional state domain**	**Mental State domain**	**Total score**
	β	**β**	**β**	**β**
Stage 1				
Age	-0.30*	-0.15	-0.13	-0.24*
Sex- male	0.27*	0.14	0.12	0.22
FEV_1	-0.07	-0.36*	-0.07	-0.21
R^2/Adjusted R^2	**0.17/ 0.13**	**0.20/ 0.16**	**0.04/ 0**	**0.16/ 0.12**
Stage 2				
Age	-0.19	-0.01	0.02	-0.08
Sex- male	0.16	-0.01	-0.04	0.06
FEV_1	-0.01	-0.29*	0.03	-0.12
Dyspnea†	0.42*	0.44*	0.68*	0.58*
Fatigue†	0.17	0.36*	0.10	0.25*
Pain†	0.01	-0.02	0.02	-0.001
R^2/Adjusted R^2	**0.45/ 0.39**	**0.71/ 0.68**	**0.57/ 0.53**	**0.74/ 0.71**
R^2 change	**0.28**	**0.51**	**0.53**	**0.57**
F change	**9.91***	**33.12***	**24.21***	**42.40***

*p-value < 0.05 †

The total scores from the DI, BFI, and BPI were used

Abbreviations: CCQ = Clinical COPD Questionnaire; FEV_1 = forced expiratory volume in one second; β = standardized regression coefficient

5.4 Discussion

This study, using parallel formatted questionnaires, found that patients with COPD have a high prevalence (greater than 70%) of dyspnea, fatigue, and pain. The magnitude and interference scores of the three symptoms were similar, with some exceptions. For example, dyspnea interfered with general activity more than pain, whilst pain interfered with mood and sleep more than dyspnea and fatigue. These three symptoms did not show any significant difference on their interference scores in other aspects of daily living. The results also revealed that these three symptoms were moderately-to-highly correlated with each other. Although the relationship between dyspnea and fatigue in patients with COPD had been previously determined,[230 276] a novel findings of this study was that pain was positively correlated with fatigue. Moreover, we found that pain was also positively correlated with dyspnea when using the parallel formatted questionnaires (the BPI and DI), which was consistent with the previous studies.[22 105] Lastly, dyspnea, fatigue, and pain were individually associated with a lower quality of life (Table 5.4). However, after controlling for confounders, only dyspnea and fatigue contributed to poor quality of life as measured by the CCQ.

Patients with COPD reported high magnitudes of the three symptoms (average scores between 4.5 and 5 out of ten) with only a couple of items differing significantly. The "worst level" of dyspnea and fatigue were greater than pain for the sub-sample that experienced all three symptoms (n = 48) and a similar pattern was shown for the entire sample (n = 96). The higher prevalence and intensities of dyspnea and fatigue may be due to their inherent relationship to the underlying pathophysiology of COPD. In patients with COPD, airflow limitation that worsens during expiration leads to lung hyperinflation, which is associated with dyspnea.[272] Lung

hyperinflation together with poor gas exchange increases the work and metabolic cost of breathing, which contribute to fatigue in COPD.[47] On the contrary, the relationship between pain and COPD is indirect and appears to be due more so to the presence of comorbidities[66 105] rather than the underlying pathophysiology of COPD. The presence of comorbidities has also been identified as a risk factor for pain.[105] Therefore, evidence to date appears to indicate that the presence of pain in patients with COPD is primarily caused by the extrapulmonary effects.[279] Pain is a significant symptom in patients with COPD, given the fact that the prevalence of pain in COPD is significantly higher than an age- and sex-matched general cohort (45% vs. 34%).[63] Also, compared to an age- and sex-matched general cohort, patients with COPD report higher pain severity scores and pain interference scores.[49] Although pain may not arise directly from COPD, its importance cannot be refuted as demonstrated by a high prevalence, and similar "average/ usual level", and "right now" magnitude domain scores compared with dyspnea and fatigue.

Dyspnea, fatigue, and pain interfered similarly among most of the aspects of daily living but there were some differences. Participants reported higher dyspnea interference scores than pain in a physical activity-related item- general activity. Conversely, the higher pain interference scores were reported in mood and sleep compared to dyspnea and fatigue. This pattern is similar to a previous study that examined dyspnea, fatigue, and pain using the DI, BFI, and BPI in lung cancer patients.[216] Dyspnea limiting exercise tolerance and physical activity in patients with COPD[268 269] can be attributed to the progressive dynamic hyperinflation that occurs when ventilation levels increase and inspiration begins before full expiration has been completed.[280] Decreased fitness and increased reliance on anaerobic metabolism can further increase

ventilation and exacerbate dyspnea during exercise and physical activity. In addition to high ventilatory demands, insidious exercise intolerance compounded by poor arterial blood gases can contribute to fatigue in patients with COPD.[47] The immediate consequences of physical activity inducing dyspnea and fatigue may explain ratings of higher dyspnea and fatigue scores on physical activity related interference items.

Higher pain interference for mood and sleep compared to dyspnea and fatigue might be related to the neurological processing of pain. Chronic pain, depression, and insomnia share similar mechanisms of brain and neurobiological patterns, which involve atrophy of the medial pre-frontal cortex, the hippocampus, and the anterior cingulated cortex.[281] It is well established that pain is a major cause of sleep disturbance in many conditions although the cause and effect of these two factors is complex.[282] Through sleep electroencephalogram activities, pain has been shown as an important factor of sleep disturbance.[283] Reciprocally, sleep deprivation and sleep interruption decreased pain thresholds.[284] Consequently, depressed mood and sleep disorders are common in individuals with chronic pain.[281] Future studies are required to determine the role of pain and specifically its contribution to depression and sleep disorders in patients with COPD.

Dyspnea, fatigue, and pain are three interrelated symptoms in COPD, which may in part be attributed their neural processing. Dyspnea, fatigue, and pain are alerting sensations that can be detected by peripheral sensory receptors and transmitted to the CNS by afferent nerves.[231] The central neural processing mechanism of dyspnea and pain involves a series of protective responses that aims to maintain homeostasis of the body.[163] Further, the perception of dyspnea and pain can activate similar brain cortical regions including the anterior insular cortex, anterior cingulate cortex and amygdala.[274] Comparatively speaking, the neurobiological mechanism

regarding the similarity of pain and fatigue have not been clarified to the same extent as dyspnea and pain. However, the theory of unpleasant symptoms claims that unpleasant symptoms, such as pain, dyspnea, and fatigue, can occur simultaneously and aggravate each other,[162] which might provide further explanation of our study results.

Dyspnea, fatigue, and pain were all individually associated with quality of life. However, the results of hierarchical regression analyses revealed that dyspnea together with fatigue explained the large majority of the variance in the CCQ scores. This result could be due to the lack of pain-related items in the CCQ. For example, the symptom domain of the CCQ includes four questions about shortness of breath, cough, and sputum. Two other commonly used disease specific health-related quality of life questionnaires used in COPD that are longer in length – the CRQ[218] and the St. George's Respiratory Questionnaire[285] did not include pain related items as well. Nonetheless, pain measured by the BPI was associated with poor quality of life evaluated by the CCQ in our study and previous studies.[49 65] Hence, considering that pain has been identified as an important symptom in COPD by several studies,[49 53 54 63 65] and pain impacts quality of life in COPD, questions querying pain should be included in COPD disease specific health-related quality of life questionnaires.

This study has some limitations. First, the use of self-reported questionnaires to evaluate symptoms and quality of life provides subjective data. However, given that dyspnea, fatigue, pain and quality of life are all subjective perceptions the use of validated questionnaires is appropriate. A second limitation is that participants with mild to very severe COPD were recruited from pulmonary rehabilitation programs in a large metropolitan centre and small communities in British Columbia, Canada. Although the prevalence of symptoms in this study is

within the range reported by other reports that did not recruit pulmonary rehabilitation participants,[24 25 65 266] it is possible that symptoms may have been more prevalent due to the nature of patients who are referred to pulmonary rehabilitation. Thus, the generalizability of our results to patients with COPD should be further explored in a more extensive sampling strategy of those who do not participate in pulmonary rehabilitation programs.

5.5 Conclusions

In summary, pain is a very prevalent symptom in patients with COPD who attend pulmonary rehabilitation programs and is only slightly less common than dyspnea and fatigue. Further, patients with COPD reported similar magnitude scores on dyspnea, fatigue, and pain. These three symptoms affect different dimensions of COPD. Dyspnea interfered with the physical activity most whereas pain interfered with attributes of mood and sleep. The three symptoms were interrelated with each other and all individually caused an impact on health-related quality of life, which highlights the fact that management of COPD should emphasize pain as well and include assessment of multiple symptoms rather than focusing on dyspnea and/or fatigue alone.

Chapter 6: The contribution of thoracic vertebral deformity and arthropathy to trunk pain in patients with COPD

6.1 Introduction

Pain is very common in patients with COPD.[49 270] In fact, it is reported at a higher prevalence and is more severe than age- and sex-matched cohorts without COPD.[49 63] Moreover, this symptom is recounted almost as commonly as dyspnea and fatigue[49 65] with COPD patients most often localizing their pain to the trunk region.[49 63 65 270] This high prevalence of trunk pain should be a consideration for clinicians because it can deter engagement in exercise and physical activity,[50] which in turn can worsen quality of life[286] and increase morbidity and mortality[214] in patients with COPD.

A potential etiology of trunk pain in patients with COPD could be related to excessive gas trapping that causes chest wall hyper-expansion, which alters the alignment of costovertebral and demi-facet joints, thus leading to symptomatic arthropathy.[128 287] It is known that abnormal joint positioning and limited range of motion can cause arthropathy and pain in the knee,[126] and similar mechanisms may contribute to arthropathy of thoracic joints and pain in patients with COPD. A second major cause of trunk pain could be osteoporosis[270] with a reported prevalence of 50% to 76% in COPD, which is significantly higher than the general population.[288] A common clinical sequela of osteoporosis is vertebral deformity (compression fracture)[113] that can result in severe back pain.

Chest computed tomography (CT) is used extensively in patients with a history of cigarette smoking for multiple investigations, such as early screening for lung cancer,[289]

evaluation of emphysema,[290] as well as detection of osteoporosis,[290] vertebral deformity, and arthritis.[291 292] The current study investigated thoracic vertebrae and thoracic vertebral joints of participants who were undergoing CT to screen for suspicious lung nodules and lung cancer. The purpose of this study was to determine if thoracic vertebral deformity and arthropathy were independent contributors to trunk pain in patients with COPD compared to individuals with a significant smoking history in the absence of COPD. We hypothesized that patients with COPD would experience more trunk pain compared with non-COPD participants with a significant smoking history. Secondly, we postulated that trunk pain in patients with COPD would be positively associated with vertebral deformity and arthropathy of intervertebral, costovertebral, and demi-facet joints.

6.2 Methods

6.2.1 Study protocol and participants

This was a cross-sectional study that primarily recruited participants from the British Columbia-Lung Health Cohort (BC-LHC) at the BC Cancer Agency and Vancouver General Hospital in Vancouver, Canada. The BC-LHC[293] is a longitudinal study that uses CT and spirometry to screen for suspicious lung nodules and lung cancer in current and ex-smokers. Another group of participants was recruited from patients receiving chest CT scans to investigate a suspicious lung nodule at St. Paul's Hospital in Vancouver, Canada. This study was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants provided written informed consent.

The inclusion criteria for this study were individuals with: (1) English fluency and over 45 years of age; (2) no cognitive or mental impairments that limited the ability to provide consent, complete the questionnaires, and perform spirometry; (3) no COPD exacerbations within the preceding two months; (4) no history of treatment for osteoporosis; (5) no thoracic spinal surgery or significant trauma that contributed to trunk pain; and (6) no scoliosis.

Immediately following the CT scans, participants completed the BPI[179] that queried pain location, intensity, and interference using 0-10 numeric rating scales. They were also asked about smoking history, BMI, and alcohol consumption. Spirometry was performed according to American Thoracic Society standards.[2]

6.2.2 Outcome measures

6.2.2.1 Brief Pain Inventory

Pain locations, pain severity and how pain interferes with daily aspects of living were self-reported by participants using the BPI.[179] Participants reported pain location by shading symptomatic regions on a body diagram. Trunk pain was defined as pain that was identified in the shoulders, chest, ribs, back, and pelvis.[294]

6.2.2.2 Chest CT scan acquisition

Chest CT scans were obtained using a multi-row detector CT scanner (at Vancouver General Hospital- Siemens Sensation 64, Siemens Healthcare, Erlangen, Germany; at St. Paul's Hospital- GE Discovery CT750 HD CT scanner, GE Healthcare, Wauwatosa WI) while the participant was positioned supine and held in full inspiration. Images were acquired from the lung apex to base using the following technical parameters: 120 kVp, 40 mAs, and 1 mm slice thickness with reconstructions performed using both a low ("b35f"- Siemens, "Standard"- GE)

and a high spatial frequency ("b60f"- Siemens, "Bone"- GE) reconstruction algorithm and the smallest field of view that contains both lungs.

6.2.2.3 Spirometry

Pre-bronchodilator lung function was measured using a portable spirometer (EasyOne™, ndd Medical Technologies, Inc., Andover MA) to determine the severity of airflow obstruction. The values of FEV_1 and FVC were collected and used to classify the severity of airflow obstruction using the GOLD diagnostic criteria of COPD.[2] As per the diagnostic criteria, participants with airflow limitation ($FEV_1/FVC < 0.7$) were assigned to the COPD group.

6.2.2.4 Vertebral deformity and spinal deformity index

Vertebral deformity was assessed from T1 to T12 at the mid-sagittal slice of each vertebra using the methodology introduced by Genant et al.[295] Briefly, CT images were reformatted into the lateral plane using 3D Slicer software package (www.slicer.org). Next, five heights were determined using the ruler function in 3D Slicer to measure the distance of the anterior (a), mid (m), and posterior (p) heights of the vertebra being assessed as well as the posterior heights of vertebrae immediately superior (p_{up}) and inferior (p_{low}) to this vertebra (Figure 6.1). Four height ratios were calculated to determine vertebral deformities: a/p, m/p, p/p_{up}, p/p_{low} and vertebral deformities were defined as any ratio less than 0.8.[295]

The spinal deformity index (SDI) was determined by summating the grade of vertebral deformity of each vertebra from T1 to T12 according to the height ratio as follows: grade 0 = normal (≥ 0.8); grade 1 = mild ($0.75 - 0.79$); grade 2 = moderate ($0.6 - 0.74$); grade 3 = severe (< 0.6).[295]

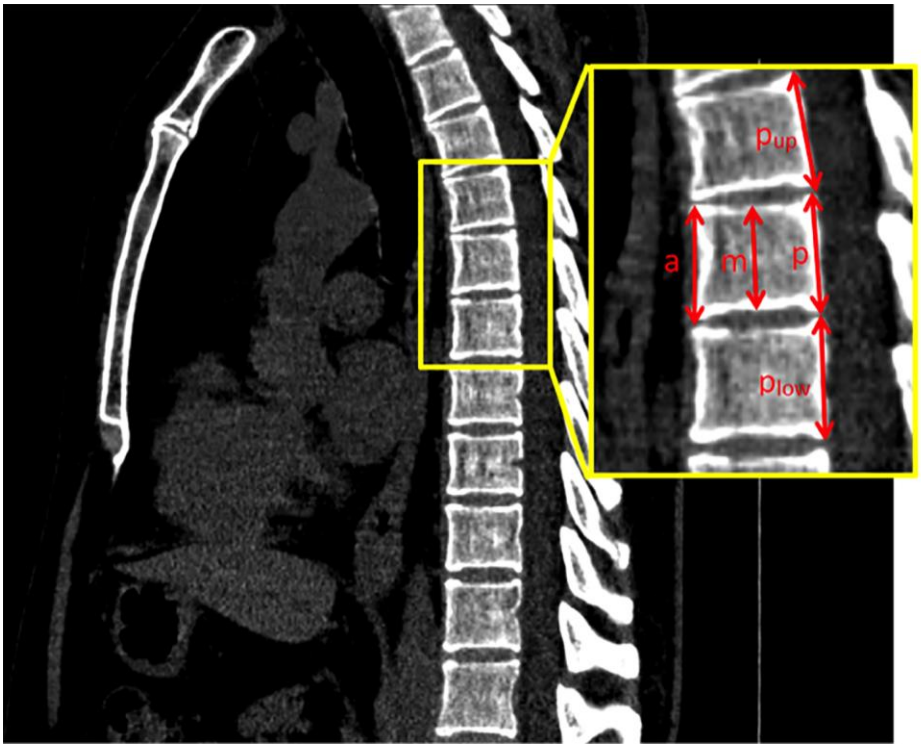

Figure 6.1 Measurements of vertebral deformity

Six points were placed on each vertebral body and vertebral heights were determined: anterior (a), mid (m), and posterior (p). p_{up} and p_{low} are the posterior heights of the vertebrae that are above and below the assessed vertebra, respectively

6.2.2.5 Arthropathy of thoracic joints

Arthropathy of costotransverse and demi-facet joints were examined by a radiologist using a semi-quantitative methodology.[292] Transverse and sagittal planes of the CT images were used to assess the arthropathy of costotransverse joints and the transverse plane was used to assess demi-facet arthropathy. Each joint was assigned a grade of 0 to 3 (0 = normal, 1 = mild, 2 = moderate, 3 = severe) by considering joint space narrowing, osteophytes, hypertrophy of the articular process, subarticular bone erosion, and vacuum phenomenon[292] (Figure 6.2). These

grades were dichotomized to absence (grade 0 or 1) or presence of arthropathy (grade 2 or 3) for the statistical analysis.

Arthropathy of intervertebral joints was assessed using a similar grading system used to evaluate arthropathy of costotransverse and demi-facet joints,[292] except intervertebral disc spaces were not included (Figure 6.3). Intervertebral disc spaces were evaluated separately using a four-grade scale: 0 = normal, disc height greater than the upper disc; 1 = slight, disc as high as the upper disc, if the upper disc height was normal; 2 = moderate, disc height narrower than the upper disc, if it is normal; 3 = severe, endplates almost in contact.[296]

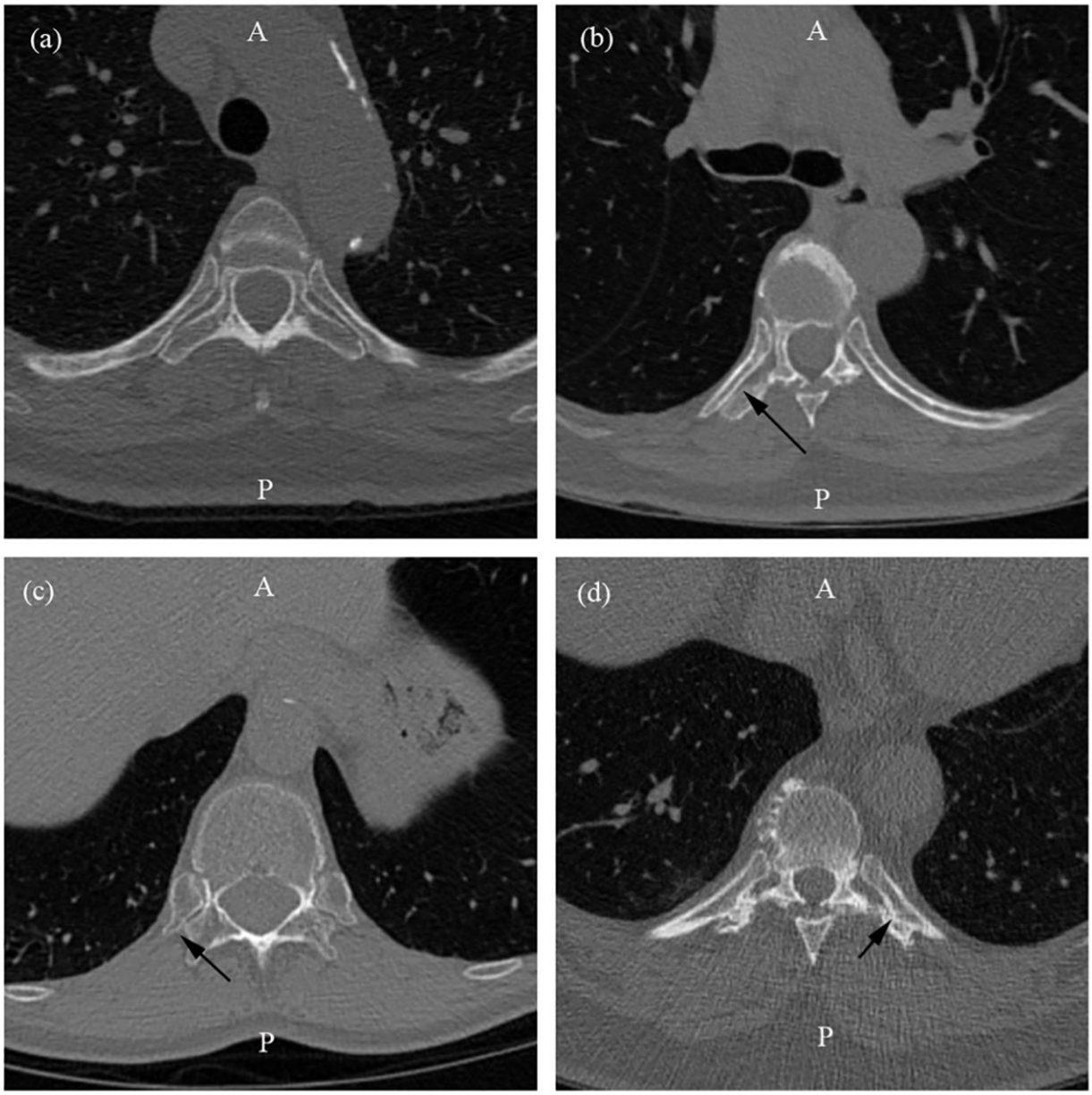

Figure 6.2 Images of arthropathy of costotransverse joints

(a) Normal, grade 0; (b) Mild, grade 1; (c) Moderate, grade 2; (d) Severe, grade 3. The black arrows showed the joint space narrowing.

Figure 6.3 Arthropathy of intervertebral joints

(a) Normal, grade 0; (b) Mild, grade 1; (c) Moderate, grade 2; (d) Severe, grade 3. The asterisks on (a) showed the normal vertebral body. The asterisks on (b), (c), and (d) showed vertebral bodies with osteophytes and vacuum phenomenon.

6.2.2.6 Bone attenuation values

The presence of osteoporosis was assessed using the densitometry measurement. Five mid-vertebral slices in the transverse plane of each vertebral body from T1 to T12 were identified. A circular region of interest that just covered the trabecular bone of the vertebral body was selected manually using ImageJ (imagej.nih.gov/ij/). The mean X-ray attenuation values measured in Hounsfield units (HU) were determined for each vertebral body. The attenuation value of a thoracic vertebra lower than 147 HU was considered to be osteoporotic.[297]

6.2.3 Intra- and inter-rater reliability

The intra- and inter-rater reliability of the measurements of vertebral deformity, arthropathy, and bone attenuation values were determined in 25 participants, measured by one assessor on two occasions and two assessors on one occasion. The ICCs demonstrated excellent intra- and inter-rater reliability (Table 6.1) and, therefore, one assessor performed all subsequent measurements.

Table 6.1 Intra- and inter-rater reliability of the outcome measurements (ICC)

Measurement	Intra-rater reliability	Inter-rater reliability
Vertebral height measurement	0.971	0.974
Costotransverse arthropathy	0.977	0.979
Demi-facet arthropathy	0.975	0.982
Intervertebral arthropathy	0.995	0.998
Intervertebral disc spaces	0.915	0.916
Bone attenuation values	0.992	0.978

Abbreviation: ICC = intraclass correlation coefficient

6.2.4 Statistical analysis

An *a priori* sample size calculation was performed based on the results of a previous study that investigated the association between vertebral deformities and back pain.[298] An odds ratio (OR) of 3.2 was assumed and a sample size of > 74 per group was calculated to provide a power of 0.9 and an $\alpha_2 < 0.05$ for logistic regression analyses.[245]

Demographic data, pain locations, the pain severity and interference scores, FEV_1% predicted values, vertebral deformities, and arthropathy were reported using descriptive statistics. Either frequencies or mean and standard deviations were reported. The difference between COPD and non-COPD groups was examined using independent sample t-tests and Chi-square tests.

Hierarchical multiple linear regression analyses were used to determine the contribution of demographic variables and measurements of vertebral deformities and arthropathy to BPI

intensity, interference, and total scores. In stage 1, demographic variables including sex, age, BMI, smoking history in pack-years, and alcohol consumption were entered in the model. The measurements of vertebral deformities and arthropathy were entered in stage 2. The associations between the presence of trunk pain and demographic variables, measurements of vertebral deformities and arthropathy were examined using multiple logistic regression analyses. Adjusted ORs of independent variables were reported. All statistical analyses were performed using SPSS (Version 22.0, Armonk, NY:IBM Corp) with a level of significance set at $p < 0.05$.

6.3 Results

Demographic and spirometric data for 171 current and ex-smokers are shown in Table 6.2. The sample had slightly more men (56%). Just over half of the study participants (53%; n = 91) were determined to have airflow limitation in the GOLD class I or above and thus, were allocated to the COPD group. Participants with COPD were about 2 years older and had a greater smoking history compared with the non-COPD group ($p < 0.05$).

Table 6.2 Demographics and outcome measures of participants

	COPD (n = 91)	Non-COPD (n = 80)	All (n = 171)
Demographics			
Sex; n (%)			
Male	51 (56%)	44 (55%)	95 (56%)
Female	40 (44%)	36 (45%)	76 (44%)
Age (yr)	68.1 (6.0)*	66.0 (6.0)*	67.1 (6.1)
FEV_1 (% predicted)	68.6 (20.1)*	89.6 (14.5)*	78.4 (20.6)
FEV_1/ FVC (%)	59.1 (10.9)*	75.7 (4.2)*	66.9 (11.9)
BMI (kg/m^2)	27.0 (5.9)	27.3 (3.8)	27.1 (5.0)
Smoking history (pack-year)	50.0 (24.7)*	40.7 (16.0)*	45.6 (21.5)
Alcohol consumption; n (%)			
Never	18 (19.7%)	13 (16.3%)	31 (18.1%)
Occasionally	45 (49.5%)	49 (61.2%)	94 (55%)
Daily	28 (30.8%)	18 (22.5%)	46 (26.9%)
Outcome measures			
Spinal deformity index	2.02 (2.72)	1.71 (2.34)	1.88 (2.55)
Arthropathy of intervertebral joints (n)	5.65 (3.20)	5.51 (3.97)	5.58 (3.57)
Disc space narrowing (n)	1.04 (1.38)	0.88 (1.19)	0.96 (1.30)
Arthropathy of costotransverse joints (n)	2.03 (2.10)	1.99 (2.10)	2.01 (2.09)
Arthropathy of demi-facet joints (n)	4.55 (2.99)	4.55 (3.08)	4.55 (3.02)
Osteoporosis (n)	6.29 (4.59)	4.90 (4.59)	5.64 (4.63)

* p-value < 0.05

Data are presented as mean (SD) or n (%)

6.3.1 Characteristics of pain

In the COPD and non-COPD groups, the majority of participants reported pain in the trunk region (29% and 35%, respectively), followed by lower extremity (24% and 23%, respectively). The prevalence of trunk pain was not significantly different between the two groups (p = 0.4). Figure 6.4 presents the number of participants who reported pain in each body location.

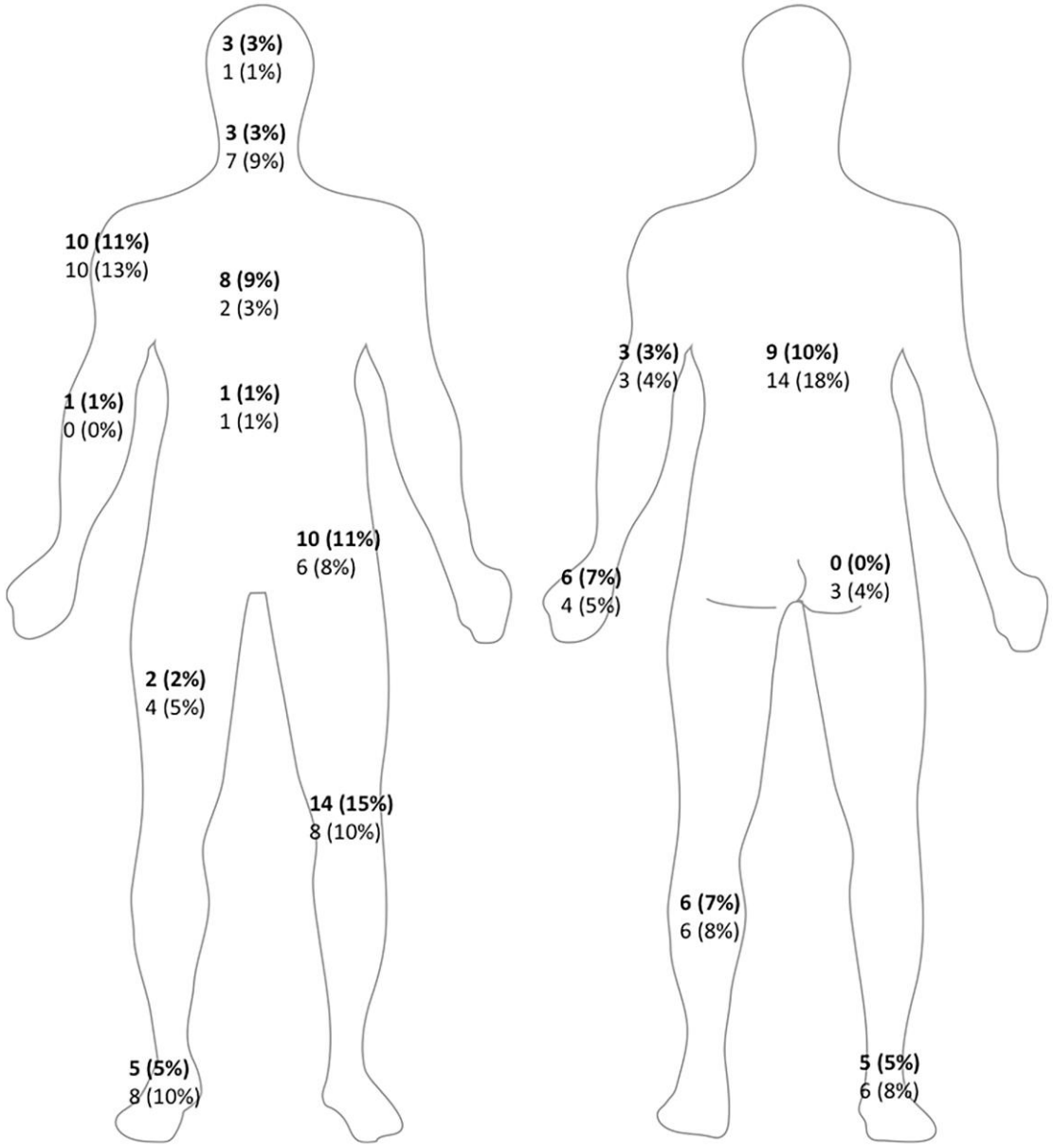

Figure 6.4 Pain locations in patients with COPD (bold) and without COPD

6.3.2 Contribution of vertebral deformity and arthropathy to the BPI scores

In the COPD group, the SDI and the number of narrowed disc spaces were significantly related to sub- and total scores of the BPI. The regression models accounted for 30%, 33% and 33% of the variance, respectively, in the BPI intensity, interference, and total scores. In the non-COPD group, higher alcohol consumption was positively related to the BPI intensity, interference, and total scores (Table 6.3).

Table 6.3 Relationships between BPI intensity, interference, and total scores and vertebral deformities and arthropathy

	COPD (n = 91)			Non-COPD (n = 80)		
	Intensity score	Interference score	Total score	Intensity score	Interference score	Total score
Variables	β	β	β	β	β	β
Stage 1						
Age	-0.20	-0.17	-0.19	-0.07	-0.10	-0.10
Sex-male	-0.15	-0.18	-0.18	-0.14	-0.14	-0.14
BMI (kg/m^2)	0.06	0.05	0.05	0.19	0.23	0.22
Smoking history (pack-year)	0.22	0.18	0.20	-0.03	0.08	0.04
Alcohol consumption-Occasionally	0.05	0.07	0.06	-0.18	-0.20	-0.20
Alcohol consumption-Never	0.13	0.15	0.15	-0.30*	-0.29*	-0.31*
R^2	**0.13**	**0.12**	**0.13**	**0.13**	**0.18**	**0.17**
F change	**1.99**	**1.86**	**1.99**	**1.88**	**2.64***	**2.48***
Stage 2						
Spinal deformity index	0.21	0.27*	0.25*	-0.19	-0.23	-0.23
Arthropathy of intervertebral joints (n)	-0.17	-0.17	-0.18	0.11	0.09	0.10
Disc space narrowing (n)	0.23*	0.29*	0.27*	0.19	0.26	0.24
Arthropathy of costotransverse joint (n)	0.20	0.19	0.19	-0.02	0.01	-0.01
Arthropathy of demi-facet joint (n)	0.07	0.05	0.06	-0.05	-0.02	-0.03

	COPD (n = 91)			Non-COPD (n = 80)		
	Intensity score	Interference score	Total score	Intensity score	Interference score	Total score
Variables	β	β	β	β	β	β
R^2	**0.30**	**0.33**	**0.33**	**0.18**	**0.26**	**0.24**
R^2 change	**0.17**	**0.21**	**0.20**	**0.05**	**0.08**	**0.07**
F change	**3.83***	**4.80***	**4.66***	**0.79**	**1.55**	**1.33**

*p-value < 0.05

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; β = standardized regression coefficient

6.3.3 The association of trunk pain with vertebral deformity and arthropathy

In the COPD group, trunk pain was associated with the presence of vertebral deformity (adjusted OR = 3.55, 95% CI = 1.18 − 10.65), the number of vertebral deformities (adjusted OR = 1.33, 95% CI = 1.00 − 1.78), and arthropathy of costotransverse joints (adjusted OR = 1.30, 95% CI = 1.04 − 1.64) after adjusting for age, sex, smoking history, and BMI. Whereas in the non-COPD group, trunk pain was only associated with alcohol consumption even when adjusted for confounders. The occasional and non-alcohol drinkers were less likely to have trunk pain compared to the daily alcohol drinkers in the non-COPD group (adjusted OR = 0.35 and 0.08, 95% CI = 0.11 − 1.13 and 0.01 − 0.74, respectively) (Table 6.4).

Table 6.4 Adjusted odds ratio of potential independent variables associated with the presence of trunk pain

Variables	Adjusted OR† (95% CI)	
	COPD (n = 91)	Non-COPD (n = 80)
Alcohol consumption		
Daily	1.00	1.00*
Occasionally	1.71 (0.50, 5.89)	0.35 (0.11, 1.13)*
Never	2.59 (0.61, 11.0)	0.08 (0.01, 0.74)*
The presence of vertebral deformity	3.55 (1.18, 10.65)*	1.29 (0.46, 3.67)
Vertebral deformity (n)	1.33 (1.00, 1.78)*	0.92 (0.68, 1.27)
Spinal deformity index	1.17 (0.98, 1.40)	0.94 (0.74, 1.19)
Arthropathy of intervertebral joint (n)	1.05 (0.90, 1.22)	1.07 (0.93, 1.23)
Disc space narrowing (n)	1.38 (0.97, 1.96)	1.28 (0.85, 1.95)
Arthropathy of costotransverse joint (n)	1.30 (1.04, 1.64)*	1.07 (0.82, 1.39)
Arthropathy of demi-facet joint (n)	1.16 (0.98, 1.38)	1.12 (0.93, 1.34)
Osteoporosis (n)	0.95 (0.87, 1.07)	0.98 (0.88, 1.10)

*p-value < 0.05

†Adjusted for age, sex, smoking history, and BMI

Abbreviations: COPD = chronic obstructive pulmonary disease; CI = confidence interval; OR = odds ratio.

6.4 Discussion

This is the first study to demonstrate that vertebral deformity and thoracic joint arthropathy are independent contributors to trunk pain in patients with COPD. Of interest, the prevalence and severity of trunk pain in the COPD and non-COPD cohorts, albeit heavy smokers, were similar in our sample. However, the contributors to trunk pain were different in the two groups. Trunk pain in COPD was associated with the presence of vertebral deformity and the number of costotransverse joints arthropathy whereas trunk pain in the non-COPD group was associated with the amount of alcohol consumption. Similar patterns were shown when considering overall pain measures. In the COPD group, the SDI and narrowed intervertebral discs were contributors to the BPI intensity, interference, and total scores whereas again higher alcohol consumption was the only significant contributor to these BPI scores in the non-COPD group.

COPD is a devastating condition, and while the primary feature of COPD is impairment of lung function, there are numerous sequelae that contribute to decreased quality of life and increased hospitalization for these patients. It has been demonstrated previously that pain is a major factor that impedes patients with COPD from engaging in exercise or physical activity.[49 50] Physical activity has been shown to be the best predictor of all-cause mortality in patients with COPD and regular exercise not only minimizes this risk but also improves quality of life and symptoms.[263] In spite of these benefits, many patients are unable or unwilling to maintain an active lifestyle[213] and pain has been shown to be associated with a lower physical activity level.[49 50] Therefore, understanding the etiology of trunk pain in COPD acts as an initial step to mitigate

the burden of this symptom, which in turn could facilitate optimization of physical activity and exercise.

The primary findings showed that trunk pain was associated with vertebral deformity and that narrowed intervertebral disc spaces and the SDI contributed to BPI sub- and total scores, which provide considerable explanation towards the etiology of pain in COPD. These results are consistent with a previous study that concluded that lumbar vertebral deformity can cause pain and the intensity of pain increases with higher degrees of deformity in the general population.[299] Vertebral deformity may lead to thoracic kyphosis in older adults, which can compromise breathing patterns by decreasing FEV_1 and vital capacity,[300] and further accentuate the overuse of respiratory muscles and exacerbate the associated pain.[301] The thoracic kyphosis can also change the alignment of the cervical and lumbar spine,[120 302] rib cage, shoulder girdle, and pelvis,[303] which could contribute to abnormal movement and chronic pain in these areas. In addition, vertebral deformities can initiate the degeneration of intervertebral discs,[304] the latter of which can elicit pain. Disc space narrowing, a primary attribute of intervertebral joint arthropathy, has been reported to be associated with pain due to degeneration of intervertebral discs and secretion of inflammatory cytokines.[305] Taken together, the ramifications of vertebral deformity and disc space narrowing can lead to several anatomical abnormalities and inflammatory responses that contribute to the presence of trunk pain in patients with COPD.

Previous studies have shown a high prevalence of osteoporosis in patients with COPD,[288] and our study reported similar findings with the average number of osteoporotic vertebrae to be 6.29 ± 4.59 in the COPD group, indicative of over half the thoracic vertebrae being affected. However, trunk pain was not associated with osteoporosis in this study, but rather vertebral

deformity. These results are consistent with the premise that osteoporosis is deemed to be a silent disease that is usually asymptomatic until subsequent fractures, such as vertebral compression fractures, occur.[112] In this study, the prevalence of vertebral deformity in patients with COPD was lower than the prevalence of osteoporosis (58% vs. 80%). Accordingly, a subsample of these COPD patients with osteoporosis is at risk to develop clinical sequelae but they may not have reached the bone density threshold or succumbed to the physical forces required to cause vertebral deformity. Therefore, the presence of osteoporosis did not account for the trunk pain experienced by the participants in the COPD group but rather its consequences, vertebral deformity.

To our knowledge, this study was the first to examine arthropathy of thoracic joints in patients with COPD. We found that it is prevalent and most importantly, arthropathy of costotransverse joints was an independent contributor to trunk pain in COPD (Table 6.4). The etiology of this arthropathy could be linked to the abnormal joint angle and restricted movement of the joints due to the hyperexpanded chest wall caused by expiratory airflow limitation and air trapping.[127] Furthermore, decreased chest wall compliance in COPD may exert higher stress forces on the costotransverse and demi-facet joints,[128] exacerbating arthropathy in these joints and accentuating pain.[126] Treatments aimed to improve chest wall mobility[306] may be effective to alleviate pain caused by thoracic joints arthropathy in patients with COPD, which needs to be studied further.

We found that participants in the non-COPD group also reported considerable trunk pain. Moreover, the prevalence of trunk pain and the BPI scores were comparable in the COPD and non-COPD groups. The participants in the non-COPD group were current or ex-smokers with the

mean smoking history of 40.7 ± 16.0 pack-years. Cigarette smoking has been reported as a risk factor for chronic pain,[307] and smokers reported a higher pain intensity score on the BPI compared to non-smokers.[308] Therefore, the significant smoking history in the non-COPD group may provide some explanation of similar pain prevalence and BPI scores in the two groups. However, unlike the relationship found between trunk pain with vertebral deformities and arthropathy in COPD, alcohol consumption was the contributor to trunk pain and BPI scores in those without COPD. Those who drink alcohol everyday were more likely to have pain and higher pain scores compared to non-drinkers. In the general population, the interdependence between chronic pain and alcohol consumption is well described.[309] It has been postulated that either the presence of chronic pain increases the level of alcohol consumption or that alcohol could lower the pain threshold.[309] Other potential factors, such as posture and obesity, which may cause trunk pain in smokers without COPD, also require further investigation.

This study has some limitations. Firstly, we did not perform dual-energy X-ray absorptiometry (DXA), which is the gold standard for diagnosis of osteoporosis. However, CT bone attenuation values are correlated with DXA[297] and previous studies have used CT as a method to assess bone densitometry.[290 297] Given the fact that the participants of this study have undergone a chest CT scan, using CT bone attenuation values derived from these images is cost-effective and avoids additional radiation exposure and burden. Secondly, this study only examined the abnormalities of thoracic vertebral articulations. Future studies that investigate soft tissue and bony structure abnormalities of the cervical and lumbar vertebrae in COPD are required in order to provide a more comprehensive explanation of trunk pain.

6.5 Conclusions

This study demonstrates that pain in the trunk region was prevalent in patients with COPD and this pain was associated with vertebral deformity and costotransverse joint arthropathy. The findings of this study provide insights into the underlying factors that contribute to trunk pain in patients with COPD. It can also be a foundation for future studies that explore the relationship between pain and anatomical structures of the other trunk areas, such as the cervical and lumbar spine in patients with COPD. This is important to clinical outcomes in this disease given that exercise plays a central role in symptomatology and quality of life in patients with COPD, while pain limits the ability of the patients to participate in exercise rehabilitation. Understanding the etiology of trunk pain is beneficial for clinicians to consider this overlooked symptom in the treatment and rehabilitation plans of COPD.

Chapter 7: Hyperkyphosis in COPD is not associated with vertebral deformities and degenerative disc disease

7.1 Introduction

Osteoporotic vertebral deformity is common in COPD with the reported prevalence ranging from 31% to 63%,[115 116] values that are significantly higher than the general population.[115] A significant cause of vertebral deformities is decreased bone mineral density. Importantly, studies have shown that COPD has several common risk factors that are associated with decreased bone mineral density including aging, smoking, and physical inactivity.[310] Therefore, people living with COPD are particularly vulnerable to vertebral deformities.[311] The clinical consequences of vertebral deformities, including pain, disability, and impaired quality of life[121] can be devastating. Moreover, vertebral deformities are also associated with height loss and increased thoracic kyphosis angles.[121 310]

Hyperkyphosis, defined as a kyphosis angle greater than 40°,[312] can result in a reduction of quality of life and several adverse health outcomes, such as impaired lung function, decreased physical function, increased fracture risk[119] and risk of mortality.[313] Hyperkyphosis has ill-defined etiologies; however, vertebral deformities and degenerative disc disease are associated with hyperkyphosis in older adults.[119] Hyperkyphosis in COPD has been postulated to be due to a variety of factors including aging, changes in chest wall alignment,[314] shortening of the pectoralis major muscle,[315] and vertebral deformities.[310 316 317] However, to our knowledge, no study has provided evidence to support these postulates.

Increased thoracic kyphosis angles are associated with pain.[318 319] This might be due to changes in the normal alignment of the cervical and lumbar spine, which in turn alters trunk posture.[119] Abnormal posture can increase stresses on the joints and muscles,[120] which may affect musculoskeletal function and cause pain.[119] The same mechanisms might also induce pain in patients with COPD who have abnormal thoracic kyphosis angles. Pain is common in COPD, with a pooled prevalence of 66%,[54] and has been most commonly reported in the trunk area.[49 53] Further, about half of patients with COPD (47%) reported that back problems were the most common comorbidity that caused pain.[270] Therefore, given that patients with COPD have greater thoracic kyphosis angles and the most common pain location is the trunk, whether hyperkyphosis is associated with trunk pain in patients with COPD warrants investigations.

The purposes of this study were to: (1) compare the thoracic kyphosis angles and the prevalence of hyperkyphosis between patients with COPD and current or ex-smokers without airflow obstruction; and (2) determine the association between hyperkyphosis with thoracic vertebral deformities, degenerative disc disease, and trunk pain in patients with COPD. We hypothesized that: (1) patients with COPD will have greater kyphosis angles as well as a higher prevalence of hyperkyphosis compared with those without COPD; and (2) vertebral deformities, degenerative disc disease, and trunk pain will be associated with hyperkyphosis in COPD.

7.2 Methods

7.2.1 Study protocol and participants

This study utilized a cross-sectional design. Current or ex-smokers were recruited from two lung cancer screening studies: (1) BC-LHC performed at British Columbia Cancer Research

Centre and Vancouver General Hospital,[293] and; (2) Patients who received a chest CT scan to examine a suspicious lung nodule at St. Paul's Hospital, Vancouver, Canada.

Participants were included if they: (1) were 45 years of age or older; (2) were fluent in English; (3) had no cognitive or mental impairments that limited their ability to provide informed consent and to complete the study; (4) had no COPD exacerbations within two months; (5) had no history of treatment for osteoporosis; (6) had no diagnosed scoliosis; (7) no history of thoracic spinal surgery or any major accident or trauma that contributed to thoracic pain.

Chest CT scans were performed on all participants, following by spirometry and the administration of the BPI. Demographic information and smoking history were also collected. This study was approved by the Clinical Research Ethics Board of the University of British Columbia. All participants provided written informed consent.

7.2.2 Outcome measures

7.2.2.1 Brief Pain Inventory

The BPI[179] was used to evaluate pain location (body diagram), pain intensity (four items), and how pain interferes with daily life activities (seven items). Participants shaded the pain areas on the body diagram and put an "X" to indicate where they experienced the most pain. Pain intensity and pain interference were assessed using 0 to10 numeric rating scales. Trunk pain was identified when participants indicated pain in the shoulders, chest, rib, back, and/or pelvis on the body diagrams.[294]

7.2.2.2 Chest CT scans

Chest CT scans were obtained using a multi-detector row CT scanner (Siemens Sensation 64 multi-slice CT scanner, Siemens Healthcare, Erlangen, Germany (Vancouver General Hospital) or GE Discovery CT 750 HD CT scanner, GE Healthcare, Wauwatosa WI (St. Paul's Hospital)) using the following technical parameters: 120 kVp and 40 mAs. Images were acquired from the base to the apex of the lung while the participant was supine and at full inspiration. Contiguous 1.0 mm (Siemens) or 1.25 mm (GE) reconstructions were performed using both low ("b35f"-Siemens, "Standard"-GE) and high spatial frequency ("b60f"-Siemens, "Bone"- GE) reconstruction algorithms and the smallest field of view that contained both lungs.

7.2.2.3 Lung function test

Pre-bronchodilator lung function was measured using a portable spirometer (EasyOne™, ndd Medical Technologies, Inc., Andover MA) according to the American Thoracic Society guidelines.[320] The values of FEV_1 and FVC were collected. Participants who had airflow limitation ($FEV_1/FVC < 0.7$) were assigned to the COPD group.

7.2.2.4 Vertebral deformity and spinal deformity index

Vertebral deformity of the thoracic vertebrae was assessed using lateral spinal CT images based on the semi-quantitative technique by Genant et al. (Figure 7.1).[295] The mid slice of each vertebra from T1 to T12 was selected using the open source software "3D slicer" (www.slicer.org). Vertebral deformities were defined when the posterior vertebral height was more than 20% lower compared to the posterior height of the adjacent vertebra or if the anterior or middle height was 20% lower than the posterior height.[295] A grade was assigned to each vertebra: grade 0 = normal (height loss < 20%); grade 1 = mild (height loss between 21% − 25%);

grade 2 = moderate (height loss between 26% − 40%); grade 3 = severe (height loss > 40%).[295] The SDI was then calculated by summing up the grade of each thoracic vertebra from T1 to T12.[295]

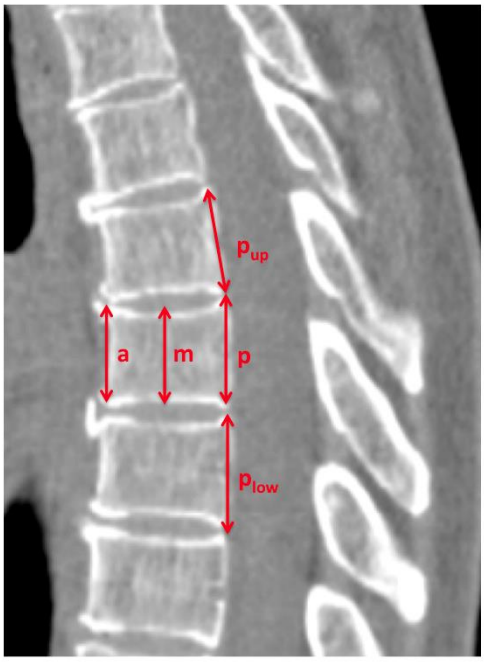

Figure 7.1 Assessment of vertebral deformity

Five vertebral body heights were measured: anterior height (a), middle height (m), posterior height (p), posterior height of the vertebra superior (p_{up}) and inferior (p_{low}) to the assessed vertebral. Height ratios were then calculated: a/p, m/p, p/p_{up}, and p/p_{low}. Vertebral deformity was defined as any ratio < 0.8.[295]

7.2.2.5 Bone attenuation value

Osteoporosis was assessed using five mid-vertebral slices in the transverse plane of the thoracic vertebral body. The mean X-ray attenuation values, measured in HU, of a circular region within the trabecular area of the vertebrae were obtained using Image J (imagej.nih.gov/ij/). Osteoporosis was defined as a mean X-ray attenuation value less than 147 HU.[297]

7.2.2.6 Disc space narrowing

Intervertebral disc space height was measured between the two midpoints of the upper and lower endplates of two adjacent vertebral bodies from T1 to T12.[321] Disc space narrowing was defined as the disc height being less than or equal to the height of upper disc.[296]

7.2.2.7 Thoracic kyphosis

Thoracic kyphosis was measured by using the Cobb technique.[322] The mid-lateral CT images were used to assess the kyphosis angle using the software "Surgimap Spine" (www.surgimap.com). The kyphosis angle was determined as the angle between the extension lines of the T1 upper endplate and T12 lower endplate (Figure 7.2). Hyperkyphosis was defined as a kyphosis angle greater than 40°.[312]

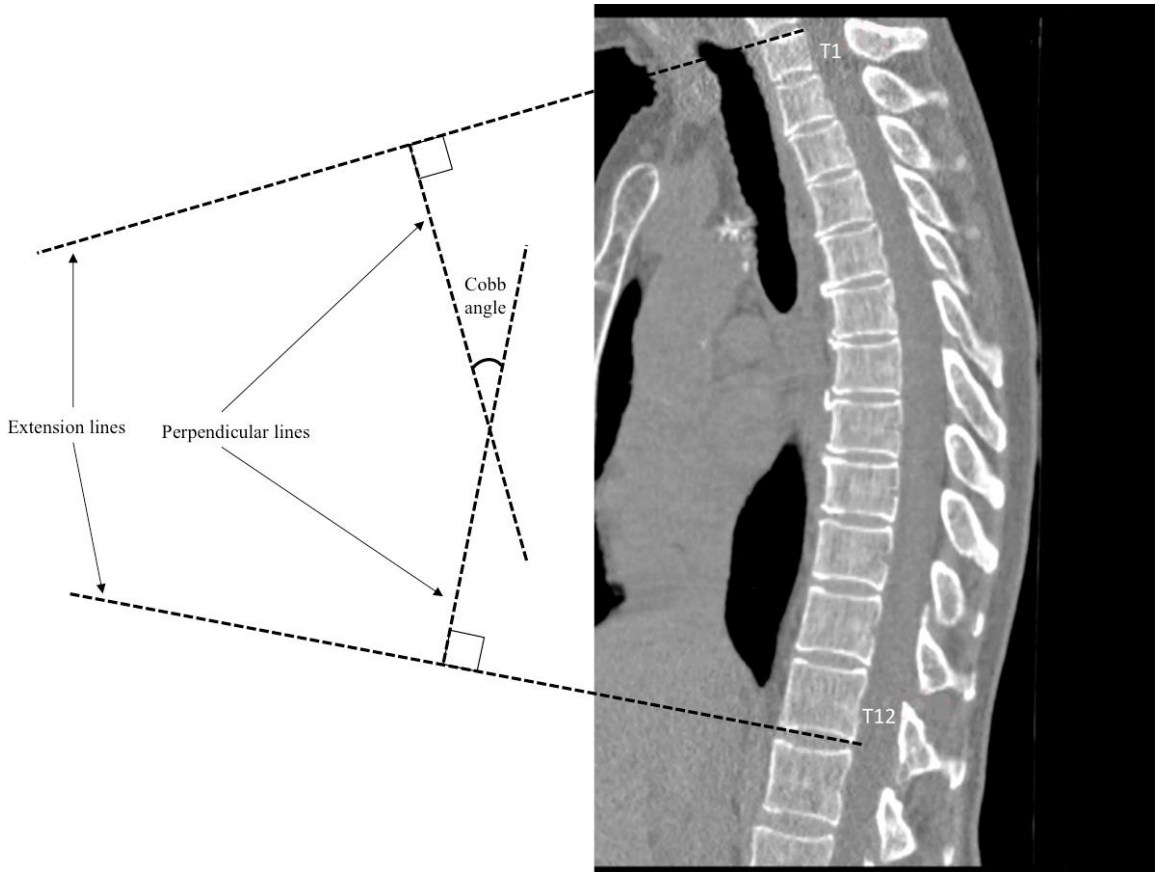

Figure 7.2 Thoracic kyphosis angle measurement

The kyphosis angle was determined as the angle between the extension lines of the T1 upper endplate and T12 lower endplate. This angle is identical to the acute angle between perpendicular lines drawn from the extension lines.[322]

7.2.3 Statistical analysis

Demographic characteristics and all the outcome measures were analyzed using descriptive statistics and reported in frequencies or mean and standard deviations. The comparisons between the COPD and non-COPD groups were examined using an independent sample t-test (continuous variables) or a Chi-square test (categorical variables). The differences in measures of kyphosis between the COPD and non-COPD groups were further examined using

multiple linear regression (continuous outcome) or multiple logistic regression analyses (binary outcome) adjusting for the confounders. Logistic regression analyses were performed to determine the association between the presence of hyperkyphosis and the measures of trunk pain, vertebral deformity, and disc space narrowing. Adjusted ORs of independent variables were reported. Statistical analyses were performed using SPSS (Version 22.0, Armonk, NY: IBM Corp). A p-value < 0.05 was set to indicate significant differences.

7.3 Results

In total, 171 participants were recruited in this study with the mean age of 67.1 ± 6.1 years old. They were all current or ex-smokers with the mean smoking history of 45.6 ± 21.5 pack-year. There were 91 participants (53.2%) in the COPD group. Participants in the COPD group were significantly older, had worse lung function, and a greater smoking history than those in the non-COPD group (Table 7.1).

Table 7.1 Demographic characteristics of participants

	COPD (n = 91)	Non-COPD (n = 80)	Total (n = 171)
Sex; n (%)			
Male	51 (56%)	44 (55%)	95 (56%)
Female	40 (44%)	36 (45%)	76 (44%)
Age	68.1 (6.0)*	66.0 (6.0)*	67.1 (6.1)
FEV_1 (% predicted)	68.6 (20.1)*	89.6 (14.5)*	78.4 (20.6)
FEV_1/ FVC (%)	59.1 (10.9)*	75.7 (4.2)*	66.9 (11.9)
Height (m)	1.71 (0.1)	1.71 (0.1)	1.71 (0.1)
Weight (kg)	79.7 (21.1)	80.7 (15.2)	80.2 (18.5)
BMI (kg/m^2)	27.0 (5.9)	27.3 (3.8)	27.1 (5.0)
Smoking history (pack-year)	50.0 (24.7)*	40.7 (16.0)*	45.6 (21.5)

* *p*-value < 0.05

Data are presented as mean (SD) or n (%)

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity

The prevalence of trunk pain was 29% and 35% in the COPD and non-COPD groups, respectively, which was not significantly different (p = 0.4). In the COPD group, the prevalence of hyperkyphosis and the kyphosis angles were significantly higher than those of the non-COPD group ($p < 0.05$). Participants with COPD were associated with an increased likelihood of hyperkyphosis (adjusted OR = 2.00, 95% CI = 1.04 − 3.84) and a greater kyphosis angle (adjusted regression coefficient = 5.49, standard error = 1.66) after adjusting for age, sex, and the

number of vertebral deformities. Vertebral deformities and disc space narrowing did not differ between the two groups (Table 7.2). The deformed vertebrae were mainly presented as wedge and biconcave deformities (38% and 60% in COPD; 40% and 60% in non-COPD, respectively) (Figure 7.3).

Table 7.2 Vertebral deformity, disc narrowing, and kyphosis in the COPD and non-COPD groups

	COPD (n = 91)		Non-COPD (n = 80)	
	Mean (SD)	Range	Mean (SD)	Range
Prevalence of trunk pain; n (%)	26 (29%)		28 (35%)	
BPI intensity score§	4.2 (1.8)	0.8 – 7.8	3.7 (1.9)	0.8 – 7.8
BPI interference score§	3.5 (2.2)	0 – 7.1	2.9 (2.1)	0.1 – 7.6
BPI total score§	3.8 (1.9)	0.7 – 6.7	3.2 (1.9)	0.4 − 7
Prevalence of vertebral deformity; n (%)	53 (58%)		43 (54%)	
Number of deformed vertebra	1.44 (1.75)	0 − 8	1.39 (1.78)	0 − 7
Spinal deformity index	2.02 (2.72)	0 − 15	1.71 (2.34)	0 − 11
Prevalence of osteoporosis; n (%)	73 (80%)*		54 (68%)*	
Number of osteoporotic vertebra	6.29 (4.59)	0 − 12	4.90 (4.60)	0 − 12
Prevalence of hyperkyphosis; n (%)	50 (55%)*		30 (38%)*	
Thoracic kyphosis angle (°)	42.9 (12.0)*	16 − 85	37.2 (10.6)*	4 − 62
Prevalence of narrowed disc spaces; n (%)	51 (56%)		37 (46%)	
Number of narrowed disc spaces	1.04 (1.38)	0 − 7	0.88 (1.19)	0 − 4

* *p*-value < 0.05

§ Calculated in those who reported trunk pain

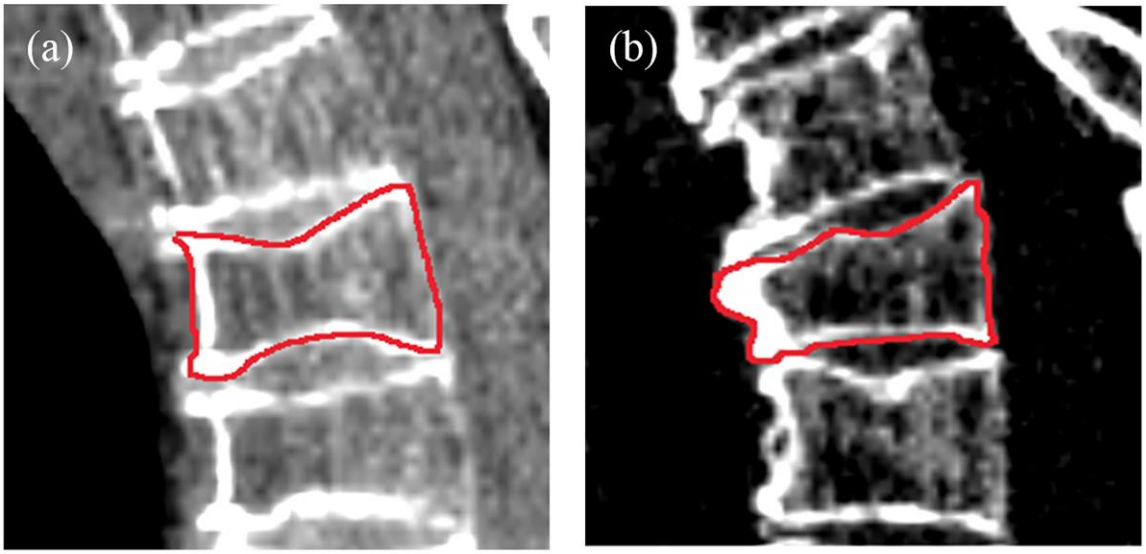

Figure 7.3 Two types of vertebral deformity

(a) biconcave: where the middle vertebral height is lower than the anterior and posterior heights; (b) wedge: where the anterior height is lower than the middle, which is lower than the posterior height.

In the COPD group, hyperkyphosis was negatively associated with FEV_1% predicted values (adjusted OR = 0.98, 95% CI = 0.96 − 1.00), and positively associated with smoking history (adjusted OR = 1.03, 95% CI= 1.00 − 1.05) as well as trunk pain (adjusted OR = 3.91, 95% CI = 1.35 − 11.3) after adjusting for age and sex. In the non-COPD group, hyperkyphosis was associated with the spinal deformity index (adjusted OR = 1.66, 95% CI = 1.22 − 2.26), the number of vertebral deformities (adjusted OR = 1.85, 95% CI = 1.32 − 2.59), osteoporotic vertebrae (adjusted OR = 1.12, 95% CI = 1.00 − 1.24), and narrowed disc space (adjusted OR = 1.71, 95% CI = 1.13 − 2.01) after adjusting for age and sex (Table 7.3).

Table 7.3 Multivariate analyses of association between hyperkyphosis and independent variables

Variables	Adjusted OR (95% CI)	
	COPD (n = 91)	Non-COPD (n = 80)
FEV_1 (% predicted)	0.98 (0.96, 1.00)*	0.98 (0.95, 1.01)
Smoking history (pk-yr)	1.03 (1.00, 1.05)*	0.99 (0.97, 1.02)
Trunk pain	3.91 (1.35, 11.3)*	0.60 (0.21, 1.63)
Vertebral deformity (n)	1.17 (0.89, 1.53)	1.84 (1.29, 2.61)*
Spinal deformity index	1.09 (0.91, 1.29)	1.66 (1.22, 2.26)*
Osteoporotic vertebra (n)	1.10 (1.00, 1.22)	1.12 (1.00, 1.24)*
Narrowed disc space (n)	0.99 (0.73, 1.34)	1.71 (1.13, 2.01)*

* *p*-value < 0.05

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; OR = odds ratio

7.4 Discussion

To our knowledge, this study is the first to investigate the association between hyperkyphosis and its potential causes, including vertebral deformities and degenerative disc disease, in patients with COPD. Also, we examined the association between hyperkyphosis and trunk pain in COPD, which has not been studied before. Our study provided evidence that the thoracic kyphosis angles and the prevalence of hyperkyphosis were significantly higher in those with COPD compared to current or ex-smokers without airflow obstruction. We also found that hyperkyphosis in COPD was associated with a greater smoking history and lower FEV_1 %

predicted values, but not vertebral deformities and degenerative disc disease. In contrast, hyperkyphosis in the non-COPD group was associated with the increased number of vertebral deformities and narrowed disc space. Of interest, trunk pain was associated with hyperkyphosis in patients with COPD but the same relationship was not observed in the non-COPD group.

We found that patients with COPD had a larger thoracic kyphosis angle than those without COPD. This result was inconsistent with two previous studies[323 324] that had small samples (n = 30 and 38). Compared with these two studies, our sample was larger (n = 171), which may have more statistical power. Also, the different techniques for measuring thoracic kyphosis angles between previous studies and ours may explain the inconsistent results. The two previous investigations[323 324] placed markers on participants' skin, photographed the positions of these markers and then calculated thoracic kyphosis angles using the extension lines from the markers. In contrast, our direct measures of thoracic kyphosis angles from chest CT images using a computer-assisted software were more valid and had excellent intra- and inter-rater reliability (ICCs = 0.99 and 0.98, respectively). In addition to a larger sample and a more direct measure of thoracic kyphosis angles, our analysis considered confounders that contribute to increased thoracic kyphosis angles, such as age, sex, and vertebral deformities. Thus, the overall comparisons between COPD and non-COPD groups in our study were more comprehensive and precise.

Our findings showed that hyperkyphosis in the COPD group was associated with a longer smoking history and lower FEV_1% predicted values. Although previous reviews have suggested that vertebral deformities are the major cause of hyperkyphosis in patients with COPD,[310 316 317] our results did not confirm this postulate and infer that hyperkyphosis in patients with COPD

might be caused by other factors, such as changes in chest wall alignment[314] or postural abnormalities.[315] Chest wall misalignment and postural abnormality may be consequences of lung hyperinflation in COPD.[128] It is well established that smoking is a major risk factor for COPD[320] and it is associated with chronic air trapping due to airflow limitation.[325 326] This in turn increases the anteroposterior diameter of the chest wall and, importantly, this altered shape of the chest wall can also be found in individuals with hyperkyphosis.[327] Moreover, the hyper-expanded chest wall can lead to shortening of the pectoralis major,[128] which can cause the forwarded shoulder posture and may increase the thoracic kyphosis angle in patients with COPD.[328]

The mechanisms that contribute to hyperkyphosis in COPD may also cause trunk pain. Changes in chest wall structure and alignment can alter the curvature of the thoracic spine and generate stress on the spine, which can induce pain.[119 120] Also, the adverse breathing pattern, which can be compounded by increased thoracic kyphosis angles,[327] can further increase the workload of the respiratory muscles as well as lead to pain. This could explain the association between hyperkyphosis and trunk pain that we found in patients with COPD. It is noteworthy that this association remained significant even after we controlled for sex, age, and vertebral deformity (OR = 3.65, 95% CI = 1.23 − 10.82), the latter of which has been shown to be associated with trunk pain in patients with COPD in our previous research.[271] This result suggested that hyperkyphosis is associated with trunk pain in patients with COPD independent of vertebral deformities. However, the causal relationship between trunk pain and hyperkyphosis remains to be determined.

Although the prevalence of osteoporosis and vertebral deformity was high (80% and 58%, respectively) in patients with COPD, they were not associated with hyperkyphosis, which is

contradictory to a previous study[329] that found a weak correlation (r = 0.26) between thoracic kyphosis angles and the presence of vertebral deformities. The earlier investigation[329] combined visual inspection with similar quantitative methods for determining vertebral deformity[295] and the thoracic kyphosis angles[322] to those used in our study. From the report, it was difficult to discern the weighting of visual observations from the quantitative measures.[329] In contrast, our study used an objective computer-assisted method to assess thoracic kyphosis angles and vertebral deformities, which can provide more precise measures. Also, our study considered potential confounders including age and sex when determining the association between hyperkyphosis with osteoporosis and vertebral deformity, whereas the previous study simply performed a correlation analysis.[329] The focus on male participants and correlation analysis may be factors that contributed to the differing results in the previous study[329] compared to our findings.

The prevalence and the contributors of hyperkyphosis in the non-COPD group are different from those with COPD. Of interest, osteoporosis, vertebral deformity, and disc space narrowing were associated with hyperkyphosis in the non-COPD group. Individuals with osteoporosis of the thoracic vertebrae are reported to have increased thoracic kyphosis angles.[330] Moreover, hyperkyphosis has been reported to be more strongly associated with thoracic than lumber vertebral deformities in the general population.[331] The more severe wedging deformities may increase the thoracic kyphosis angles and, in turn, lead to hyperkyphosis.[117] Our study also found that the narrowed intervertebral disc was another contributor to hyperkyphosis in the non-COPD group. This is consistent with the results from previous studies that reported the presence of degenerative disc disease to be associated with increased kyphosis angles.[332] [333] It is

noteworthy that the degeneration of intervertebral disc and vertebral deformities are associated with each other. Disc space narrowing has been found to be a risk factor for vertebral deformities[334] and vertebral deformities appear to initiate the process of intervertebral disc degeneration.[304] Therefore, both osteoporotic vertebral deformities and degenerative disc disease have combined influences on thoracic kyphosis angles among individuals without COPD.[117]

A limitation of this study was that thoracic kyphosis angles using CT images were obtained in the supine position, which may not be the preferred upright position for kyphosis measurements. However, there was a significant correlation between standing and supine measures of thoracic kyphosis angles.[335] Also, a supine position can be the favored position for kyphosis measurements, especially in older adults.[119] [335] Second, other factors that may contribute to hyperkyphosis in patients with COPD were not examined, such as the length and strength of respiratory muscles, and lung hyperinflation. Consequently, the relationship between hyperkyphosis with the abnormal posture and/or chest morphology requires further investigation in patients with COPD. Lastly, our study did not draw a conclusion about the causality of hyperkyphosis and trunk pain due to the cross-sectional study design. However, the results of this study confirmed the association between hyperkyphosis and trunk pain and provided future studies a foundation regarding the investigation of pain etiology in patients with COPD.

7.5 Conclusions

This study confirmed that patients with COPD have larger thoracic kyphosis angles and a higher prevalence of hyperkyphosis compared to those in the non-COPD group. Moreover, the associations with other anatomic and clinical features are quite different between the two groups.

Worthy of note, thoracic vertebral deformities and degenerative disc disease were not the major contributors to hyperkyphosis in patients with COPD. This lung disease per se may lead to changes in lung and chest wall structures, which in turn increase the risk of hyperkyphosis and trunk pain. Future studies regarding the association between hyperkyphosis and changes in chest wall alignment as well as posture abnormality in COPD are required.

Chapter 8: Conclusion

This chapter summarizes the major findings of each chapter, the strengths and limitations of the thesis as well as the overall thrust of the thesis.

8.1 Summary of the findings

Pain is a common symptom in patients with COPD, which is associated with several adverse health outcomes, including reduced physical activity levels,[49 69] impaired exercise capacity,[50] and poor quality of life.[50 64 65 68] Current studies have investigated the prevalence, characteristics, and clinical impacts of pain in patients with COPD. However, the causes of pain in patients with COPD are not fully understood, which may limit specific treatment strategies to address pain. Also, unlike dyspnea and fatigue, recommendations regarding the assessment and management of pain are not included in the current COPD guidelines,[1 3 38] which may underappreciate the recognition and the importance of treating pain in the overall management plan of COPD.

The causes of pain are likely complicated and multifactorial in patients with COPD. This dissertation aimed to investigate the causes of pain in patients with COPD through identifying the comorbidities that cause pain and the contributors to pain, determining the interactions between pain and other symptoms, as well as examining the associations between pain and musculoskeletal structure abnormalities. The following sections in 8.1 summarize the rationales, major findings, discussion, and future directions of each study.

8.1.1 Reliability and validity of the BPI in patients with COPD (Chapter 2)

To date, there is no standardized assessment tool to evaluate pain in patients with COPD. The most commonly used pain questionnaire in COPD studies is the BPI even though the reliability and validity of the BPI had not been determined in this group of patients. Given the fact that a reliable and valid questionnaire can yield more accurate results and robust evidence, the objective of Study I in this dissertation was to determine the reliability and validity of the BPI in patients with COPD.

This study found that the BPI demonstrated excellent internal consistency and test-retest reliability in patients with COPD, indicating that the individual items in the BPI measure the same construct and are able to produce consistent results. The results of examining construct validity of the BPI revealed that four of the eleven items in the BPI loaded into one factor and the remaining seven items were grouped into the other factor, which supports that the BPI is a two-dimensional (pain magnitude and pain interference) questionnaire. The results of investigating convergent and divergent validity of the BPI showed that the correlations between the BPI and short-form MPQ scores were moderate to good, whereas the BPI correlated poorly with all domains of the SF-36, except bodily pain. These results exhibited that the BPI and short-form MPQ measure the same construct, i.e. pain. In contrast, the SF-36 is a health-related quality of life questionnaire and, therefore, the underlying construct of the domains is different from that in the BPI. Lastly, the BPI exhibited the discriminant validity by showing the ability to distinguish pain levels among COPD patients with different levels of quality of life and physical activity.

In conclusion, the overall findings of this study indicate that the BPI is a reliable and valid questionnaire that can be used to evaluate pain in patients with COPD. The BPI is a short and easily administrated pain questionnaire that can capture information on pain magnitude as well as how pain interferes with aspects of daily living. The simple scoring system of the BPI allows the extensive use of this questionnaire in clinical and research settings. The BPI appears to be a valuable screening tool and overall descriptor of pain whereas other methodologies could provide more detail about the specific etiology and cause of pain e.g. qualitative interviews, imaging of anatomical structures. Future studies are required to investigate the responsiveness of the BPI to demonstrate its ability to detect changes due to intervention, which is more relevant to the purpose of clinical use.

8.1.2 Reliability and validity of the BFI and DI in patients with COPD (Chapter 3)

Besides pain, dyspnea and fatigue are two common symptoms in patients with COPD.[21 25-29] In order to better understand how these three symptoms interact with each other and their relative severity and interference in patients with COPD, we proposed to use questionnaires with uniform formats to assess pain, dyspnea, and fatigue. The BFI and DI, two questionnaires with a parallel format to the BPI, were used to evaluate fatigue and dyspnea, respectively. The reliability and validity of both the BFI and DI had not been determined in patients with COPD. Therefore, the objective of Study II in this dissertation was to establish the reliability and validity of the BFI and DI in patients with COPD.

The BFI and DI demonstrated good internal consistency and test-retest reliability. The items in the magnitude and interference domains of the BFI and DI can measure the same concept, i.e. fatigue and dyspnea, respectively. Also, both the BFI and DI are able to generate

similar results between two tests. With respect to validity, this study examined construct, concurrent, and discriminant validity of the BFI and DI. The results of construct validity analysis showed that all the items in the BFI and DI were loaded into one factor, indicating that the items of each questionnaire measured the intended construct, i.e. fatigue and dyspnea, respectively. Compared with the CRQ, a well-established questionnaire that is used to assess fatigue and dyspnea in patients with COPD, the BFI showed high whereas the DI had moderate to high concurrent validity. Lastly, the BFI and DI did not show discriminant validity. Both questionnaires could not distinguish the levels of dyspnea or fatigue among individuals with different COPD severities. However, given the fact that the purposes of the BFI and DI are to evaluate symptoms rather than discriminate COPD severity, both questionnaires are still considered valid even though they failed to demonstrate discriminant validity.

In conclusion, this study found that the BFI and DI are two reliable and valid questionnaires for patients with COPD. Similar to the BPI, both the BFI and DI are simple questionnaires for patients with COPD to self-report symptom severity and how symptoms interfere with different aspects of daily life activities. Similar to the BPI, the BFI and DI do not delve deeply into underlying causes except queries about aspects of daily living. However, the parallel items of the BPI, BFI, and DI allow researchers and/or clinicians to readily compare pain, dyspnea, and fatigue as well as to better understand the relative severity and interference scores of these three symptoms in patients with COPD. Future studies are suggested to establish the responsiveness of the BFI and DI. As well, discriminant validity of the BFI and DI could be determined among COPD patients with different levels of physical performance and/or quality of life.

8.1.3 Comorbidities that cause pain and the contributors to pain in patients with COPD (Chapter 4)

Whereas Chapters 1 to 3 provide foundations for the thesis research, Chapters 4 to 7 address the crux of this thesis – What are underlying causes of pain in COPD patients? The primary objectives of Study III (presented in Chapters 4 and 5) were to investigate, using a survey design, the comorbidities that cause pain and secondly, to examine the association between pain and fatigue as well as pain and dyspnea in patients with COPD.

It has been reported that pain in patients with COPD is associated with the presence of comorbidities,[50 66 105] but the specific comorbidities that cause pain are not known. In order to explore the etiology of pain, this study investigated the comorbidities that cause pain as well as determined the demographic, physical, and psychological contributors to pain in patients with COPD. To perform this survey study, we used validated questionnaires from studies I and II along with questionnaires that asked about demographics, socioeconomic status, self-efficacy, comorbidities that cause pain, and the use of medications.

This study found that 71% of our participants with COPD reported pain. The trunk was the most commonly reported location of pain, followed by the lower extremity, which is in accord with previous studies.[27 62 63 67-69] Approximately 87% of participants with pain reported more than one comorbidity that caused pain and on average, each participant with pain had four comorbidities that caused pain. The most common comorbidities that caused pain were arthritis, followed by back problems and muscle cramps. Among the participants of this study, both lower self-efficacy, and renting rather than owning a house independently increased the likelihood of having pain. Also, a higher BFI total score contributed to a higher BPI magnitude score.

Similarly, a higher BPI magnitude score along with a higher BFI total score contributed to a higher BPI interference score, which confirmed that pain is associated with fatigue in patients with COPD.

This study is the first to identify comorbidities that cause pain in patients with COPD and in particular, musculoskeletal conditions account for the majority of pain in patients with COPD. Previous studies have confirmed that among musculoskeletal diseases, osteoporosis[109 110] and osteoarthritis[50 104] are two highly prevalent comorbidities in patients with COPD. Therefore, the association between pain and osteoporosis as well as osteoarthritis should be further examined to provide insight into the causes of pain in COPD. Secondary findings suggest that COPD patients with higher self-efficacy may have better coping abilities in response to adverse events and thus, have better pain control strategies.[256 257] Housing situation (renters versus home owners), one indicator of socioeconomic status, was also found to be associated with the presence of pain in this study. In addition to physical factors, socioeconomic status and psychological factors (i.e. depression and anxiety) may also play an important role in the presence and perception of pain. This current study focused more on physical factors (i.e. comorbidities and other COPD symptoms) and did not use specific questionnaires or diagnosis tools to reveal more detailed information on socioeconomic status and psychological factors. Therefore, future studies that comprehensively examine the associations between pain and socioeconomic status as well as psychological factors are worthwhile. Developing clinical practice guideline strategies that bridge management of common comorbidities and COPD are also essential.

8.1.4 A comparison of pain, fatigue, dyspnea and their impact on quality of life in pulmonary rehabilitation participants with COPD (Chapter 5)

Dyspnea and fatigue are two symptoms that have been comprehensively investigated in COPD and the association between these two symptoms has been previously reported.[230 276] Moreover, the link between pain and dyspnea has been established by brain imaging studies[165-171] as well as clinical studies in patients with COPD.[22 105] Comparatively speaking, the relationship between pain and fatigue in patients with COPD is under-investigated. In addition, pain, dyspnea, and fatigue are three commonly reported symptoms in patients with COPD. Exploring the relative prevalence and magnitude of these three symptoms, how each symptom interferes with aspects of daily living, and their impact on quality of life in the same group of participants can facilitate a greater understanding of the similarities and differences among pain, fatigue, and dyspnea. Therefore, the work described in Chapter 5 further compared pain, dyspnea and fatigue and examined the interrelationships among these three symptoms, using questionnaires with parallel formats, in patients with COPD.

The data from this study showed that more than 70% of patients with COPD reported symptoms of pain, dyspnea, and fatigue. As expected, the prevalence of dyspnea was the highest (93%) in patients with COPD, followed by fatigue (77%) and pain (74%). The magnitude scores of these three symptoms were similar (4.5 to 5.0 out of 10). Dyspnea and fatigue were significantly higher than pain in the “worst level” item scores among patients with COPD who reported having all the three symptoms. Also, dyspnea interfered with general activity more than pain, whereas pain interfered with mood and sleep more than dyspnea and fatigue. These three symptoms were interrelated. The total BPI scores had a moderate-to-high correlation with the

total DI and BFI scores. Lastly, the BPI, DI, and BFI scores were individually associated with quality of life measured by the CCQ. However, when considering the effects of all the symptoms together on quality of life, only dyspnea and fatigue were the significant contributors to the CCQ scores.

In conclusion, the magnitude and interference scores of pain, dyspnea, and fatigue were similar in patients with COPD with some exceptions, which emphasizes the fact that pain is a distinctive symptom. Compared with dyspnea and fatigue, pain can impact different aspects of daily living in patients with COPD. We also concluded that pain, dyspnea, and fatigue are interrelated with each other. Our findings corroborate the theory of unpleasant symptoms,[162] which claims that unpleasant symptoms can be present concurrently and worsen each other. Although we found that pain, dyspnea, and fatigue were all individually associated with quality of life, pain appears to be insignificant when taking into account all three symptoms. This result is likely due to the fact that the questionnaire used to measure quality of life (CCQ) does not include pain related items. Also, other quality of life questionnaires commonly used in patients with COPD do not include any items querying pain. Given that pain is prevalent in COPD and it can affect quality of life in patients with COPD, pain should be included in COPD disease-specific quality of life questionnaires in the future.

Overall, Study III, presented in Chapter 4 and Chapter 5, provided evidence regarding the contributors to pain, comorbidities that cause pain, and the importance of pain in patients with COPD compared to the more commonly reported symptoms of dyspnea and fatigue.

8.1.5 The contribution of thoracic vertebral deformity and arthropathy to trunk pain in patients with COPD (Chapter 6)

The work in Study IV is presented in Chapter 6 and Chapter 7 and used advanced imaging analysis of the thoracic spine to explore the causes of pain. Building on the results of Study III, the associations between trunk pain and two specific musculoskeletal comorbidities (vertebral deformity and arthropathy) were further investigated in Study IV.

Trunk pain has been reported by patients with COPD as the most common location of pain.[27 62 63 67-69 270] The potential etiology of trunk pain in patients with COPD could be linked to arthropathy and osteoporotic compression fractures in the spine. Lung hyperinflation in patients with COPD can lead to changes in chest wall structures,[287] which could cause joint misalignment and increase arthropathy. Also, the predisposition to osteoporosis among patients with COPD[310 311] could contribute to a high prevalence of vertebral deformity. In order to determine the association between trunk pain and thoracic spine abnormalities, this cross-sectional study administered the BPI and performed spirometry to current or ex-smokers to evaluate their pain and the levels of airflow obstruction as well as performed CT image analysis of the thoracic spine to inspect thoracic vertebral deformity and arthropathy of joints between the ribs and spine.

The results of this study showed that the trunk area was the most commonly reported location of pain in both the COPD and non-COPD groups. Also, the BPI scores as well as the average number of vertebrae that have osteoporosis, deformities, and arthropathy were similar between the COPD and non-COPD groups. Nonetheless, the contributors to trunk pain were different between the two groups. The presence of trunk pain in patients with COPD was associated with the presence of vertebral deformity, the number of vertebral deformities, and

arthropathy of costotransverse joints. The same associations were not observed in the non-COPD group. Instead, trunk pain was associated with the amount of alcohol consumption in current or ex-smokers without COPD. Similarly, the SDI (a composite measure of vertebral deformity) and the number of narrowed disc spaces were positively related to the BPI magnitude, interference, and total scores in patients with COPD, whereas alcohol consumption was positively associated with the sub- and total scores of the BPI in the non-COPD group.

In conclusion, this study is the first to examine the relationships between trunk pain and anatomical structures of the thoracic vertebrae as well as thoracic vertebral joints in patients with COPD. The findings of this study suggest that osteoporotic vertebral deformity and arthropathy in joints of the chest wall contribute to trunk pain in patients with COPD. Of interest, although the prevalence of osteoporosis in patients with COPD was high (80%), it was not associated with trunk pain, which exemplifies that osteoporosis is frequently asymptomatic until fractures occur.[112] This study provides an initial step to investigate the underlying factors that cause trunk pain in patients with COPD. Future studies that scrutinize the associations between trunk pain and anatomical structures of cervical and lumbar vertebrae can offer more evidence towards unravelling the puzzle of trunk pain in patients with COPD. Evaluation of soft-tissue structures, such as shortened inspiratory muscles and increased tension of these muscles would be worthwhile.

8.1.6 Hyperkyphosis in COPD is not associated with vertebral deformities and degenerative disc disease (Chapter 7)

It is generally regarded that osteoporotic vertebral deformity is associated with increased thoracic kyphosis angles in older adults.[119] Consequently, it is implied that hyperkyphosis in

patients with COPD may be due to the same underlying cause[310 316 317] given the fact that osteoporotic vertebral deformity is very prevalent in COPD.[115 116] Other postulated contributors to increased thoracic kyphosis angles in patients with COPD are aging, changes in chest wall alignment,[314] and postural abnormality.[315] However, no clinical studies have been conducted to verify these assumptions. Of equal consideration, increased thoracic kyphosis angles are associated with pain.[318 319] Therefore, the objective of this study was to determine the associations between hyperkyphosis and thoracic vertebral deformity, degenerative disc disease, and trunk pain in patients with COPD utilizing CT image analysis and BPI scores.

The prevalence of hyperkyphosis and thoracic kyphosis angles were significantly higher in patients with COPD compared with current or ex-smokers without COPD. The presence of COPD was associated with the increased risk of having hyperkyphosis and increased thoracic kyphosis angles. In patients with COPD, hyperkyphosis was associated with FEV_1% predicted values and a greater smoking history rather than vertebral deformities. In contrast, hyperkyphosis was associated with the SDI, the numbers of vertebral deformities, osteoporotic vertebrae, and narrowed disc space in the non-COPD group. Lastly, trunk pain in COPD was associated with hyperkyphosis.

In conclusion, patients with COPD have higher thoracic kyphosis angles than those without COPD. Worthy of note, hyperkyphosis in patients with COPD appears to be caused by factors other than vertebral deformities. We found that COPD per se is a risk factor for hyperkyphosis. Thus, the associated lung hyperinflation in COPD that induces alterations in chest wall structures, such as shortening of the pectoralis major and minor, might contribute to increased thoracic kyphosis angles. Similar mechanisms may, in part, lead to trunk pain

associated with hyperkyphosis in patients with COPD. Of interest, vertebral deformity was not associated with increased kyphosis angles as expected in patients with COPD, which may suggest that hyperkyphosis could occur independent of vertebral deformities. The etiology of hyperkyphosis in patients with COPD requires further investigation.

Taken all together, Study IV provides evidence of the associations between trunk pain and thoracic vertebral deformity, arthropathy, and hyperkyphosis, which sheds light on potential causes of trunk pain in patients with COPD.

8.2 Strengths and limitations

The major strengths of this dissertation are the novelty of study questions and rigorous research methods. No studies to date had investigated underlying causes of trunk pain. To our knowledge, no studies had determined the reliability and validity of the BPI, BFI, and DI in patients with COPD (Studies I and II). Moreover, Study III is the first study to investigate comorbidities that cause pain in patients with COPD as well as to compare the three of the most common symptoms of COPD. Similarly, Study IV is the first to explore the etiology of pain in patients with COPD by examining bony structures of the thorax. Importantly, since the symptoms of COPD are assessed subjectively, we established the reliability and validity of the pain, dyspnea, and fatigue questionnaires in patients with COPD and used these validated questionnaires in Studies III and IV, which solidifies the persuasiveness of this study. Furthermore, in Study IV, abnormalities of thoracic vertebrae and joints as well as thoracic kyphosis angles were assessed using objective computer-assisted measures. In addition, the intra-

and inter-rater reliability were pre-established for all the measurements, i.e. image analysis measures, which greatly underpins the research quality.

Taken together, this dissertation advances the field of pain research in patients with COPD. Pain is a complex issue and the causes of pain are very likely multifactorial in patients with COPD. The studies in this dissertation built upon current knowledge, pain theories, and recent evidence of pain in patients with COPD. The findings of this dissertation regarding the contributors to pain and etiology of trunk pain in COPD facilitate a deeper understanding of this issue and warrant development of pain management strategies in the overall care of these patients.

This dissertation also has some limitations. The primary limitation of this dissertation is that participants were recruited as samples of convenience, which may limit the generalizability of the study results to COPD patients outside of Canada and in some cases to patients who did not participate in pulmonary rehabilitation programs. Although no evidence indicates any differences between patients with COPD who do and those do not attend pulmonary rehabilitation programs as well as among patients with COPD in different countries, regarding their symptoms, comorbidities, and clinical outcomes, the interpretation of the results to patients with COPD outside of this sample must be approached with caution. Also, these studies collected most of the data (i.e. symptoms and comorbidities) using self-reported questionnaires, which can be less objective than other measures. However, as mentioned above, since pain and most of the outcomes in the studies are subjective perception, self-report by participants is an appropriate way to obtain the information. It is for these reasons, therefore, that the questionnaires were rigorously evaluated in Studies I and II before being applied in Studies III and IV. Besides, in

Study III, comorbidities that caused pain were self-reported by participants and further cross-validated by health professionals, which would provide more accurate information.

8.3 Contributions and potential applications

Pain is a significant symptom in patients with COPD but unlike dyspnea and fatigue, it has not been extensively studied nor included in the current COPD clinical practice guidelines.[1 3 38] Also, pain has been underappreciated and neglected in clinical settings even though patients with COPD deem this symptom as a barrier to full participation in pulmonary rehabilitation programs[52] or regular physical activity.[49 50] The research in this dissertation sheds light on the causes of pain, which have not received in-depth attention previously. The novel findings of the four studies in the dissertation can bring new information to researchers' and clinicians' attention as well as promote a better understanding of pain in COPD. First, based on the results of Study I and Study II, the BPI, DI, and BFI are reliable and valid symptom assessment tools and, therefore, can be used in clinical settings as well as for research purposes in patients with COPD. Second, the results from Study III and Study IV provide evidence on the causes of pain, which can afford the foundation for defining pain interventions, designing rehabilitation programs that include strategies to alleviate pain, and facilitating the development of pain assessments and treatments in the overall management of COPD. The overall contributions of this dissertation are to fill the gap in the current pain research in patients with COPD and enlighten future research in this area.

One of the goals of my PhD research is to facilitate evidence-based clinical decision making in this area, which would involve the application of knowledge translation strategies.

The Canadian Institutes of Health Research defines knowledge translation as "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system. This process takes place within a complex system of interactions between researchers and knowledge users which may vary in intensity, complexity and level of engagement depending on the nature of the research and the findings as well as the needs of the particular knowledge user".[336] The knowledge to action process of our research findings mainly involves end of grant knowledge translation,[336] which aims to apply research findings into clinical practice and ensure that knowledge users, i.e. health care providers, clinicians, patients, policy makers, are aware of our research findings.[337] Based on the Canadian Institutes of Health Research, there are five key elements of an end of grant knowledge translation plan: goals, audience, strategies, expertise, and resources.[338] Focusing on two audience groups, health professionals and patients, the next two paragraphs describe potential knowledge translation plans of this PhD research.

For clinicians and health care providers, the goal of the knowledge translation plan is to raise awareness of pain and its association with particular comorbidities in patients with COPD. Using typical and traditional methods to present research findings can help convey the concepts and ideas of our research to this audience group. For example, publishing papers in journals, giving short talks or oral presentations in workshops and conferences, and writing commentaries or articles in health-related magazines and/or on COPD- or pulmonary disease-related websites. Delivering education and training sessions for health professionals is another knowledge translation strategy to disseminate the research findings into practice. Most

importantly, pain should be included in the current COPD clinical practice guidelines, which can facilitate and strengthen the recognition of this symptom in COPD. Another practical application might be to provide a seminar about the Brief Pain Inventory to health professionals so they know how to use a useful screening tool for incoming patients

For patients with COPD and their family, the goal of the knowledge translation plan is to deliver the basic knowledge of pain in COPD and encourage patients to report pain to health professionals. The knowledge of pain and the results of the research should be delivered using a plain language. Patients with COPD should be aware that pain is prevalent and this lung disease and several medical conditions that are associated with pain may occur at the same. Pain is a subjective perception. Therefore, patients with COPD should be educated in effective ways to report and describe their pain to health professionals. The research findings can be disseminated using brochures, posters, and educational materials that are available at hospitals, COPD clinics, and pulmonary rehabilitation centres. Pulmonary rehabilitation programs can include an education session that introduces pain and some of its underlying causes. During this session, patients with COPD could be encouraged to ask questions. Moreover, social media is an effective venue to translate research evidence to clinical practice.[339] Therefore, the information regarding pain in COPD should also be available online.

8.4 Future directions

This dissertation is an initial step to reveal the potential causes of pain in patients with COPD. Several future research directions are suggested to disentangle the puzzle of pain in COPD. First, the associations between trunk pain and other physiological factors, such as the

overuse of respiratory muscles, changes in morphology of chest wall, and cervical and/or lumbar vertebral abnormalities, require further investigation in order to provide more comprehensive insight into trunk pain. Studies with a longitudinal design can provide better information on the causal relationships between these physiological factors and trunk pain in patients with COPD. Also, future research on how psychological conditions (i.e. depression and anxiety) affect pain perception in patients with COPD would be worthwhile.

Second, future research directions should focus on the development of trunk pain interventions in patients with COPD. The findings of Study IV suggested that the changes in chest wall structures might further cause arthropathy of thoracic joints and hyperkyphosis, both of which are associated with pain. It has been shown that passive stretching[340] and joint manipulation[341] can increase muscle flexibility and improve joint stiffness. Previous studies have determined the effectiveness of cervical spine manipulation on pain and joint range of motion.[341-343] Therefore, passive stretching and joint manipulation may be effective interventions to improve clinical outcomes in patients with COPD. For example, the effects of a passive respiratory muscle stretching technique on improving chest wall mobility, chest wall volumes, respiratory muscle tension, and dyspnea in patients with COPD have been reported in previous research.[344 345] Furthermore, chest wall stretching, a technique that contains the concepts of muscle stretching, thoracic manipulation, and mobilization,[346] has been shown to be beneficial for improving lung function, the ability of chest expansion, and dyspnea levels in patients with COPD.[346-348] However, the standardized protocol of chest wall stretching has not been formally developed for patients with COPD. Also, the effects of this technique on improving trunk pain in patients with COPD have not been studied yet. Therefore, well-designed randomized controlled

trials should be conducted in the future to determine optimal protocols of this intervention (e.g. frequency, duration, and intensity) as well as its immediate and long-term benefits on ameliorating trunk pain in patients with COPD.

Third, based on the results of Study III, pain in patients with COPD is associated with dyspnea and fatigue. It would be interesting to investigate whether COPD patients with dyspnea and/or fatigue had a higher prevalence of pain than those without dyspnea and/or fatigue. Also, it would be worthwhile to examine the effectiveness of the interventions or treatments on multiple symptoms in patients with COPD. There is growing evidence that pain and dyspnea share similar physiological[165-171] and psychological features.[173 174] However, the neurobiological mechanisms between pain and fatigue are still unclear. Moreover, sleeplessness is a commonly reported symptom in patients with COPD.[21 24-28] It has been suggested that pain and sleeplessness may be interrelated[282 284] but this relationship has not been fully examined in patients with COPD. Therefore, future studies should focus on these unknown research questions in order to elucidate the associations among pain and other symptoms in COPD.

Fourth, to our knowledge, the current disease-specific quality of life questionnaires for patients with COPD, e.g. the CCQ,[239] CRQ,[218] and St. George's Respiratory Questionnaire,[285] do not include pain related items. Given the fact that pain is a common symptom in COPD patients that can negatively impact the quality of life,[50 64 65 68] a COPD disease-specific quality of life questionnaire that includes items querying pain should be developed in the future.

Lastly, research on the potential contributors to pain in the body regions other than the trunk area in patients with COPD is worthwhile. For instance, lower extremity is the second-ranked common pain location in our sample. Pain in this region may also have a huge impact on

physical functions, daily life activities, and health outcomes. As a result, exploring the etiology of lower extremity pain could consolidate the current evidence and improve health outcomes.

8.5 Conclusions

This dissertation explored the pain experience, contributors, and causes of pain, specifically trunk pain, in patients with COPD. The work in this dissertation brings new information into clinical and research settings as well as broadens the current knowledge regarding the etiology of pain in patients with COPD. Pain in COPD is complex and can be triggered and/or accentuated via several pathways, including the occurrence of certain comorbidities, changes in chest wall structures, interactions among symptoms, and psychological factors. The findings of this dissertation open the door for future pain research as well as offer an evidence-based foundation for the development of optimal rehabilitation strategies to improve pain in patients with COPD.

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Appendix

Appendix A Forms and questionnaires*

A.1 Follow-up Screening Questionnaire (Study II)

Follow-up Screening Questionnaire

Please indicate how you would describe your COPD compared to when you completed the initial questionnaire package by **circling** the most appropriate answer below:

Worsened Stayed the Same Improved

*The following questionnaires did not include in Appendix A because of copyright issues: Brief Pain Inventory, Brief Fatigue Inventory, Dyspnea Inventory, Clinical COPD Questionnaire, and General Self-Efficacy Scale.

A.2 Participant information form (Study III)

PARTICIPANT INFORMATION

Subject Code: …… Date of birth (yyyy/mm): .....

Sex: …… Height: …… Weight: …….

Age: …….. Birth place (city and country): ……

Circle the best answer

1. What is your highest level of education?
   1) High school
   2) College or diploma at university (3 years or less)
   3) University bachelor's or baccalaureate degree (4 years)
   4) University masters or doctorate
   5) Professional degree i.e. nursing, engineering, medicine, health professional, dentist, other

2. What is your living status at home?
   1) I live with family members that need my support i.e. financial, physical and emotional
   2) I live with family members that can provide support i.e. financial, physical and emotional

3. What is your work status?
   1) Paid work (full/part time)
   2) Unpaid work
   3) Unable to work due to illness or disability.
   4) Retired, do not do any work in or outside of the home.

4. What type of work do you do?
   1) Desk job where I am sitting most of the day.
   2) Light activity that involves a combination of walking, standing or sitting but I do not do moderate or heavy labor
   3) Moderate labor i.e. house cleaning, lifting less than 20 lbs
   4) Heavy labor that requires lifting or moving heavy objects
   5) Unable to work due to illness or disability
   6) Retired

5. What is your housing situation?
   1) I rent an apartment or house
   2) I own/ have a mortgaged house or apartment

A.3 List of health conditions that might contribute to pain (Study III)

RECORD OF HEALTH CONDITIONS AND MEDICATIONS **Subject's code: _____**

Please check √ **all medical conditions** that **cause you pain for longer than the past three months**.

Indicate the date that this condition first caused you pain or the date of diagnosis.

Check √ the box *Date of onset or date of diagnosis*

- ❑ Have you had pain that has persisted for longer than the last three months? _____
- ❑ Do you have chest pain or angina due to a heart condition? _____
- ❑ Do you have disease of the blood vessels in your legs that cause calf pain when walking? _____
- ❑ Have you ever broken bones or had joints replaced that cause you pain? _____
- ❑ Do you have pain and stiffness in your joints that hurt more when you walk or when you use the painful joints? For example, arthritis? _____
- ❑ Do you have chronic fatigue syndrome or fibromyalgia? _____
- ❑ Do you have a problem in your back that causes you pain? For example, a slipped disc? _____
- ❑ Do you have a problem in your neck that causes you pain? _____
- ❑ Do you have compression fractures in your back because you have brittle or fragile bones, also known as osteoporosis? _____
- ❑ Do you have complications from diabetes that cause problems with the nerves in your hands, feet or elsewhere in your body that cause you pain? _____
- ❑ Do you have problems with the nerves in your hands, feet or elsewhere in your body that cause you pain? For example, shingles? _____
- ❑ Do you have frequent tension headaches or migraines? _____
- ❑ Do you have pain elsewhere in your head or face? If so, do you know the cause? _____
- ❑ Do you have heart burn or pain at the back of your throat or the middle of your chest from eating spicy or fatty foods? _____
- ❑ Do you have cancer or the after effects of treatment for cancer that causes you pain? _____
- ❑ Do you get muscle cramps that cause moderate to severe pain? _____
- ❑ Has the doctor or psychologist told you that you have an anxiety disorder? _____
- ❑ Do you suffer from depression sometimes? _____

Do you have any other major health problems that cause you pain? If so, can you list them in the space below?

_____

_____

Are you currently smoking? _____If not, did you smoke in the past? _____

How many cigarettes were you or are you smoking per day? _____

When did you start smoking? _____ When did you quit smoking? _____

A.4 Medication record form (Study III)

Subject's code: _____ Date: _____

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.

NAME	DOSE	FREQUENCY	START DATE
Aspirin	20 mg	Twice a day	July, 2007

A.5 Participant information form (Study IV)

PARTICIPANT INFORMATION Subject Code: …… Date: ……..

Sex: …… Height: …… Weight: …… Age: ……..
Birth place (city and country): …….

Circle the best answer

1. What is your highest level of education?
   1) High school
   2) College or diploma at university (3 years or less)
   3) University bachelor's or baccalaureate degree (4 years)
   4) University masters or doctorate
   5) Professional degree i.e. nursing, engineering, medicine, health professional, dentist, other

2. What is your living status at home?
   1) I live with family members that need my support i.e. financial, physical and emotional
   2) I live with family members that can provide support i.e. financial, physical and emotional
   3) Living alone

3. What is your work status?
   1) Paid work (full/part time)
   2) Unpaid work
   3) Unable to work due to illness or disability
   4) Retired, do not do any work in or outside of the home

4. What type of work do you do?
   1) Desk job where I am sitting most of the day.
   2) Light activity that involves a combination of walking, standing or sitting but I do not do moderate or heavy labor
   3) Moderate labor i.e. house cleaning, lifting less than 20 lbs
   4) Heavy labor that requires lifting or moving heavy objects
   5) Unable to work due to illness or disability
   6) Retired

5. What is your housing situation?
   1) I rent an apartment or house
   2) I own/ have a mortgaged house or apartment

6. Recent COPD illness (needing antibiotics or hospitalization) within the last 2 months?
   1) Yes
   2) No
   3) Not applicable (Not diagnosed with COPD)

7. History of (Circle all that apply)
   1) Scoliosis (curving of the spine to the side) that needed major medical treatment
   2) Surgery in the neck or back
   3) Major accident or injury to the chest, neck or back

8. Undergoing or underwent any of these treatments? (Circle all that apply)
   1) For brittle /weak bones*; If yes, Name of medication_____; When it was taken (year) _____ to_____*
   2) Hormone replacement; *If yes, Name of medication_____; When it was taken (year) _____ to _____*
   3) Oral corticosteroids; *If yes, Name of medication_____; When it was taken (year) _____ to _____*

9. Alcohol consumption:
   1) Never
   2) Occasionally
   3) Daily