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Fatigue, Physical Performance, and Systemic Inflammation
in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

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Patients with chronic obstructive pulmonary disease (COPD) often experience multiple symptoms, which are highly interrelated. Symptom burden in COPD affects physical and mental health negatively. Fatigue is the second most prevalent symptom after dyspnea in COPD. It is increasingly recognized as a key symptom and clinical indicator of functional limitation among COPD patients. Although the underlying mechanism of fatigue is still unknown, recent studies suggests that inflammation may play a role in development of fatigue. The aim of this dissertation study was to examine influencing factors and impacts of fatigue for patients with COPD. It was part of a longitudinal observational study of COPD patients to examine the biological causes and functional consequences of depression. In the first paper, we examined

interrelationships among dyspnea, anxiety, depressive symptoms, and fatigue as contributing factors of physical performance in COPD. We found that dyspnea was the strongest predictor of impaired physical performance. Greater anxiety was associated with enhanced physical performance. Dyspnea was associated with anxiety, and depression, and fatigue, and anxiety and depression were associated with fatigue. These findings showed that multiple symptoms are interrelated to each other. Furthermore, symptoms experienced by COPD patients have impacts on physical performance. Longitudinal studies are needed to confirm the directionality of these relationships. The second study was performed to explore the association between systemic inflammation and fatigue over one year in patients with COPD. Four inflammatory markers were included C-reactive protein (CRP), interleukin-6 (IL-6), IL-8, and tumor necrosis factor - α . IL-8 and CRP were associated with fatigue after adjusting for potential confounders when using baseline data. However, the longitudinal data analyses did not show any associations between systemic inflammation and fatigue. It indicates systemic inflammation may play a role in the development of fatigue in COPD. The CRP may serve as a potential biomarker of fatigue in COPD. Depressive symptoms are closely associated with fatigue among COPD patients. Further studies are needed to confirm the role of inflammatory biomarkers in the development of fatigue. Findings of this dissertation study can be used to develop an exercise intervention to improve symptom burden for the COPD population.

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Chapter 1. Introduction

Significance of the Problem

Chronic obstructive pulmonary disease (COPD) is a common respiratory illness that affects more than 80 million people, approximately 10% of the adult population worldwide (Buist et al., 2007). It is characterized by chronic airflow limitation caused by a mixture of obstructive bronchiolitis and emphysema (Global strategy for diagnosis, 2015). By 2020, COPD is projected to become the third leading cause of disability, and fifth leading cause of death globally (Global strategy for diagnosis, 2015; Lopez & Murray, 1998). Currently, it is the third leading cause of death in the United States (Lopez & Murray, 1998). Adults with COPD experience high rates of healthcare uses due to acute exacerbations, impaired functional status, and symptom distress (Buist et al., 2007; Mollaoglu, Fertelli, & Tuncay, 2011).

The majority of people with COPD experience multiple symptoms including dyspnea, anxiety, depression, and fatigue. These symptoms are highly interrelated (Kapella, Larson, Patel, Covey, & Berry, 2006; Park & Larson, 2014; Park, Meldrum, & Larson, 2013). Dyspnea and fatigue tend to interact with each other, and both are associated with anxiety and depression (Kapella et al., 2006; Lopez & Murray, 1998; Maurer et al., 2008). Recent studies show that complex, bidirectional relationships exist among these four symptoms (Kapella, Larson, Covey, & Alex, 2011; Mollaoglu et al., 2011; Park et al., 2013; Stridsman, Mullerova, Skar, & Lindberg, 2013). Fatigue is the second most prevalent symptom after dyspnea in COPD, and is a major complaint of COPD patients as the disease progresses (Park et al., 2013; Walke et al., 2007). Although the prevalence of fatigue is 50-71% in people with COPD (Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009; Park & Larson, 2014; Park et al., 2013), the clinical relevance of fatigue has received less investigation compared to dyspnea (Paddison, Effing,

Quinn, & Frith, 2013). Fatigue is a prominent disease-related symptom from the patient's perspective that adversely affects activities of daily living (Blinderman et al., 2009). It is defined as "a subjective, unpleasant symptom that incorporates total body feelings, ranging from tiredness to exhaustion, creating an unrelenting overall condition, which interferes with individuals' ability to function to their normal capacity" (Ream & Richardson, 1997). Furthermore, muscle weakness and decreased exercise capacity are associated with fatigue (Lewko, Bidgood, Jewell, & Garrod, 2014; Mollaoglu et al., 2011; Todt et al., 2014). In COPD, fatigue is increasingly considered to be a key symptom and clinical indicator of reduced physical activity (Park & Larson, 2014; Stridsman, Lindberg, & Skar, 2014).

COPD patients often experience impaired physical performance compared to healthy controls (Altenburg et al., 2013; Kapella et al., 2006). Reduced physical activity has a negative impact on health outcomes in COPD (Altenburg et al., 2013; Park et al., 2013; Todt et al., 2014). Patients with moderate to severe COPD report experiencing notable dyspnea and fatigue with activities of daily living (Todt et al., 2014). Psychological stress, possibly resulting from dyspnea, in combination with fatigue may contribute to impaired physical performance (Kapella et al., 2006; Paddison et al., 2013; Park et al., 2013). A vicious cycle of symptom-induced immobility leads to muscle weakness and decreased physical capacity (Altenburg et al., 2013; Bossenbroek, de Greef, Wempe, Krijnen, & Ten Hacken, 2011; Gimeno-Santos et al., 2014) leading to worsening symptoms, social isolation, and increased risk of COPD exacerbations (Gimeno-Santos et al., 2014; Park et al., 2013). The identification of contributing factors to physical performance has the potential to enhance the overall medical management of COPD patients.

Persistent, low-level, systemic inflammation is observed in some COPD patients (Agusti et al., 2012; Agusti & Sin, 2014; Barnes, 2009; Global strategy for diagnosis, 2015). Multiple cytokines play a key role in developing chronic inflammation in COPD, such as C-reactive protein, interleukin-6 (IL-6), IL-8, and tumor necrosis factor - α (Al-shair et al., 2011; Barnes, 2009; Gan, Man, Senthilselvan, & Sin, 2004). Those systemic inflammatory markers were significantly increased among individuals with COPD compared with healthy control groups (Gan et al., 2004). Recently, it has been suggested that these pro-inflammatory cytokines act in the brain to induce sickness behaviors including depression and fatigue (Al-shair et al., 2011; Dantzer & Kelley, 2007; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Systemic inflammation is also associated with impaired lung function, impaired physical performance, mortality, COPD exacerbations, and extrapulmonary comorbid conditions (Gan et al., 2004; Lu et al., 2013; MacNee, 2013; Man et al., 2006; Sethi et al., 2012). However, whether systemic inflammation is present among COPD patients, and whether it is related to symptoms, including fatigue, is controversial (Al-shair et al., 2011; Dantzer et al., 2008; Gan et al., 2004; Lewko, Bidgood, & Garrod, 2009). Examining these potential relationships is needed to understand the pathophysiologic mechanism involved in COPD.

Recent systematic reviews showed that worsening symptoms and systemic inflammation tend to be associated with reduced physical activity based on unidimensional approaches or cross-sectional studies (Bossenbroek et al., 2011; Gimeno-Santos et al., 2014). Therefore, structural equation modeling is needed to explore complex interrelationships between symptom experiences and physical performance. Furthermore, regression analyses using longitudinal data are needed to examine the potential association between fatigue and inflammation in order to better understand the mechanism of fatigue in COPD. The results of this dissertation study will

clarify the factors that contribute to physical health in patients with COPD, and help in the design of future intervention studies to better manage fatigue.

Statement of the Study Purpose

There are two main aims to this study:

1. To examine interrelationships among dyspnea, depression, anxiety, and fatigue as contributing factors to physical performance in COPD patients.
2. To examine an association between inflammation and fatigue over one year in COPD patients.

Content of the Dissertation

The dissertation consists of two parts. In Chapter 2 (Aim 1), findings from structural equation modeling analyses of the relationships between dyspnea, anxiety, depressive symptom, fatigue, and physical performance are presented. This study provides insights for symptom management to improve physical performance for the COPD population.

Part two (Chapter 3, Aim 2) of the dissertation reports findings from longitudinal data analyses of the relationship between systemic inflammation and fatigue. Changes in fatigue symptoms over one year are explored by examining inflammatory markers and potential biobehavioral confounders.

Finally, a summary of the two studies is included in Chapter 4. This chapter concludes with a discussion on symptom science focusing on fatigue in order to develop new interventions to alleviate fatigue symptoms.

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Chapter 2

Effect of Symptoms on Physical Performance in COPD

Abstract

Background: Chronic obstructive pulmonary disease (COPD) patients experience multiple symptoms including dyspnea, anxiety, depression, and fatigue, which are highly correlated with each other. Psychological stress may result from dyspnea, and psychological stress and fatigue may contribute together to impaired physical performance. **Aim:** The purpose of this study was to examine interrelationships among dyspnea, anxiety, depressive symptoms, and fatigue as contributing factors of physical performance in COPD. **Methods:** This study includes baseline data from a longitudinal observational study of COPD patients to explore the relationship between depression, inflammation, and functional status. Dyspnea was measured with Chronic Respiratory Questionnaire (CRQ), the Modified Medical Research Council Dyspnea Scale, and the Shortness of Breath Questionnaire. Anxiety was measured with the Hospital Anxiety and Depression Scale (HADS), two questions from the CRQ-Emotional Functioning, and one question from Mental Health Subscale of the SF-36. Depression was measured with the HADS and the Patient Health Questionnaire-9. Fatigue was measured with the Vitality Subscale of the SF-36 and CRQ. Physical performance was measured with the six minute walk test, average daily total steps, the Physical Functioning and the Role Physical Subscales of the SF-36. Data analyses including confirmatory factor analyses and structural equation modeling were conducted. **Results:** Dyspnea, anxiety and depression had direct effects on fatigue as well as dyspnea and anxiety had direct effects on physical performance for COPD

patients. Greater dyspnea was significantly associated with impaired physical performance.

Greater anxiety was significantly associated with enhanced physical performance. **Conclusions:**

Dyspnea was the strongest predictor of impaired physical performance in patients with moderate to severe COPD. Longitudinal studies are needed to confirm the directionality of these relationships between common symptoms and physical performance in COPD.

Keywords: dyspnea, anxiety, depression, fatigue, physical performance, COPD

Introduction

The majority of people with chronic obstructive pulmonary disease (COPD) experience multiple symptoms including dyspnea, anxiety, depression, and fatigue. These common symptoms are interrelated (Kapella, Larson, Patel, Covey, & Berry, 2006; Park & Larson, 2014; Park, Meldrum, & Larson, 2013). For COPD patients, dyspnea is the most frequent symptom that needs to be managed every day. The experience of breathing discomfort is not only a physical symptom, but also characterized as psychological, social, and environmental experiences (ATS, 1999; Carrieri-Kohlman et al., 2010). Fatigue is the second most prevalent symptom after dyspnea, and becomes a major complaint of COPD patients as the disease progresses (Park et al., 2013; Walke et al., 2007). Although the prevalence of fatigue is 50-71% in people with COPD (Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009; Park & Larson, 2014; Park et al., 2013), the clinical relevance of fatigue has received less investigation (Paddison, Effing, Quinn, & Frith, 2013). Fatigue is a prominent disease-related symptom from the patient's perspective that adversely affects activities of daily living (Blinderman et al., 2009). COPD patients described fatigue symptom as unrelenting tiredness and exhaustion that is always present, and thus it limited their previous function and capacity (Disler et al., 2014; Stridsman, Lindberg, & Skar, 2014). In COPD, fatigue is increasingly considered to be a key symptom and clinical indicator of functional limitation (Park & Larson, 2014; Stridsman et al., 2014). Anxiety and depressive symptoms are major comorbidities in COPD. Psychological distress have negative impacts on pulmonary function, exercise capacity, and fatigue symptom. It also predicts hospitalization due to exacerbation and mortality (Di Marco et al., 2006; Yohannes & Alexopoulos, 2014).

According to the Theory of Unpleasant Symptoms (TOUS), there are influencing factors and consequences that are related to one or multiple symptoms (Lenz, Suppe, Gift, Pugh, & Milligan, 1995). The model shows that multiple symptoms are often experienced at the same time. Performance of multiple symptoms as outcome or effect may include both functional and cognitive activities, for example, physical activity and concentrating on tasks. The theory also suggests that reciprocal relationships of influencing factors, multiple symptoms, and performance of symptoms may exist (Lenz, Pugh, Milligan, Gift, & Suppe, 1997).

Dyspnea and fatigue tend to interact with each other. Both symptoms are associated with anxiety and depression (Kapella et al., 2006; Lopez & Murray, 1998; J. Maurer et al., 2008). Recent studies show that complex, bi-directional relationships exist among those common symptoms of COPD (Kapella, Larson, Covey, & Alex, 2011; Mollaoglu, Fertelli, & Tuncay, 2011; Park et al., 2013; Stridsman, Mullerova, Skar, & Lindberg, 2013). Patients with moderate to severe COPD report experiencing notable dyspnea and fatigue with activities of daily living (Todt et al., 2014). Psychological stress may result from dyspnea, and psychological stress and fatigue may contribute together to impaired physical performance (Kapella et al., 2006; Paddison et al., 2013; Park et al., 2013). Anxiety, depression and fatigue are potential mechanisms through which dyspnea may impair physical performance. Researchers can target these mechanisms to understand how to enhance physical performance for patients with COPD.

The identification of contributing factors to physical performance has the potential to enhance symptom management for COPD patients. Structural equation modeling (SEM) allows researchers to examine the complex interrelationships among multiple variables (Kline, 2010). A previous research performed path analysis to examine symptoms in COPD patient, but their approach used limited numbers of measurements for symptoms (Kapella et al., 2006). SEM has

less restrictive assumptions considering measurement error compared to path analysis. By using several variables for constructs of symptoms and physical performance, the present study extends research in COPD that has shown conflicting associations among major symptoms with physical performance.

The major aim of this research is to examine a model describing the interrelationships among dyspnea, anxiety, depressive symptoms, and fatigue as contributing factors of physical performance in COPD. The model was developed based on qualitative studies of fatigue in COPD and the Theory of Unpleasant Symptoms (Disler et al., 2014; Stridsman et al., 2014). SEM was used to test the direct and indirect effects of four major symptoms on physical performance. The following hypotheses were tested: 1) higher level of dyspnea is associated with higher levels of anxiety, depression, and fatigue, and higher levels of anxiety and depression are associated with higher level of fatigue; 2) higher levels of dyspnea, anxiety, depression, and fatigue are associated with impaired physical performance; and 3) greater dyspnea is indirectly associated with greater fatigue and impaired physical performance through greater anxiety and depression, and greater anxiety and depression are indirectly associated with impaired physical performance through fatigue.

Methods

This study is a part of a prospective observational study of COPD patients to explore the relationship between depression, inflammation, and functional status. The data used in this study were collected at baseline assessment. The written informed consent was obtained from all participants at baseline visit, and the study was approved by the respective institutional review boards at three clinical sites.

Procedure

Participants were recruited from various sources including outpatients clinics from the three medical centers, pulmonary rehabilitation programs, a research database maintained by the investigators, queries of medical records and pulmonary function tests, Better Breathers Club, community pulmonary practices, advertisements, study website, and other referrals. Baseline study assessments were conducted both in person (spirometry, six minute walk test, activity monitoring, hand grip strength, and completion of questionnaires) and by telephone. Phone visits with a trained mental health professional were scheduled two days after the in-person visit and included assessment of depression and anxiety.

The inclusion criteria of this study were: 1) Diagnosis of COPD confirmed by the following: 1-a) post-bronchodilator Forced Expiratory Volume in one second to Forced Vital Capacity ratio (FEV1/FVC) < 70%; 1-b) moderate to very severe disease by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (FEV1 < 80%), 2) Age \geq 40 years, 3) A history of current or past cigarette smoking (> 10 pack-years), 4) Stable disease with no acute exacerbations in the past 4 weeks, and 5) Ability to speak, read and write English. Patients with any of the following conditions were excluded: other chronic obstructive lung diseases, idiopathic pulmonary fibrosis, uncompensated congestive heart failure, primary pulmonary vascular disease, non-COPD-related chronic inflammatory diseases, infectious disease or autoimmune disease, lung cancer or metastatic cancer, chronic renal failure that requires dialysis, chronic uncompensated liver disease, HIV/AIDS, chronic antibiotic use or ongoing infection, chronic oral prednisone use, bipolar disease, psychotic disorders, and any dementia.

Measures

The latent constructs in the model of this study were dyspnea, anxiety, depression, fatigue, and physical performance. At least two indicator variables were used for each construct that is assumed theoretically to determine them, as described below (Figure 2.1).

[Figure 2.1 about here]

Physical performance. Four indicators were used to measure the latent variable, physical performance. First, the six minute walk test (6MWT) was used according to the American Thoracic Society (ATS) guidelines (Laboratories, 2002). It is a valid measure of functional capacity in COPD patients. Distance in feet that patients walked during six minutes was used. Second, daily total steps measured by a Stepwatch activity monitor was used. Participants were asked to wear the Stepwatch fastened above the right ankle for one week. The average of total steps a day more than three days was calculated and that was used. The Stepwatch monitor has been validated for in COPD patients. The last two indicators were two subscales of the Medical Outcomes Study Short Form-36 (SF-36) questionnaire: Physical Functioning and Role Physical (McHorney, Ware, & Raczek, 1993). Scores may range from 0 to 100, higher scores indicating higher levels of physical performance.

Dyspnea Symptom. Three indicators were used to measure the latent variable, dyspnea. First, Chronic Respiratory Questionnaire (CRQ) was used to measure dyspnea (Guyatt, Berman, Townsend, Pugsley, & Chambers, 1987). The CRQ is a widely used tool to measure COPD-specific health-related quality of life in four domains (dyspnea, fatigue, emotional function, and mastery). CRQ-dyspnea is a 5-item scale with a range of 1 = extremely short of breath to 7 = not at all short of breath. Scores may range from 5 to 35, higher scores indicating lower levels of dyspnea. Second, the University of California, San Diego Shortness of Breath Questionnaire (SOBQ) was used (Eakin, Resnikoff, Prewitt, Ries, & Kaplan, 1998). It rates dyspnea associated

with activities of daily living. This 24-item scale tool ranges from 0 = not at all to 5 = maximal or unable to do because of breathlessness. Scores may range from 0 to 120, higher scores indicating higher levels of dyspnea. Third, the modified Medical Research Council (mMRC) dyspnea score was used (Global strategy for diagnosis, 2015). It is a simple grading system for dyspnea with a range of 0 (I only get breathless with strenuous exercise) to 4 (I am too breathless to leave the house or I am breathless when dressing).

Depressive Symptom. Two measures were used for depression. First, the Patient Health Questionnaire (PHQ)-9 measures current depression (Kroenke, Spitzer, & Williams, 2001). This 9-item scale ranges from 0 to 27. Participants with a score ≥ 10 were considered to have a high likelihood of major depression. Second, the Hospital Anxiety and Depression Scale (HADS) was used (Zigmond & Snaith, 1983). It is a widely used instrument to assess the severity of psychological stress. It is a 14-item scale with a range of 0-3 that consists of depression and anxiety, each with 7 items. A score of 8 or higher on either scale indicates clinically relevant anxiety (HADS-A) or depression (HADS-D). HADS-D was used as a second indicator of depression.

Anxiety Symptom. Four measures were used for anxiety. First, HADS-A was used. Higher score indicates higher anxiety. Second, one item (“Have you been a very nervous person?”) from the Mental Health Subscale of SF-36 questionnaire was used. It ranges from 1 to 6. Third, two items from CRQ-emotional function were used. Two questions are “How much of the time during the last 2 weeks did you feel relaxed and free of tension?” and “In general, how often during the last 2 weeks have you felt restless, tense, or uptight?” Both ranges from 1 to 7. For three individual items, higher scores indicates less anxiety.

Fatigue Symptom. Two indicators were used to measure the latent variable, fatigue: the CRQ-fatigue and the Vitality subscale of the SF-36. The CRQ-fatigue is a 4-item scale with a range of 1 = extremely fatigue to 7 = not at all fatigue. It may range from 7 to 28, higher scores representing less severe fatigue. The SF-36 Vitality Subscale was used. It is a 4-item subscale with 2 positively worded items (“Did you feel full of pep?” and “Did you have a lot of energy?”) and 2 negatively worded items (“Did you feel worn out?” and “Did you feel tired?”). Scores may range from 0 to 100, higher scores indicating higher levels of vitality.

Disease severity. Disease severity was categorized using the forced expiratory volume in one second (FEV1). Two groups were defined as either moderate (FEV1 \geq 50% predicted) or severe (FEV1 < 50% predicted) COPD.

Statistical Analysis

For easier interpretation of the values of each indicator, some variables were recoded so that higher scores of each measurement show greater levels of symptom and better physical performance. Data analyses were conducted in two steps using Stata 13.0 (StataCorp LP, College Station, Texas). The first step was to perform confirmatory factor analyses (CFA) for the latent variables having more than two indicators (dyspnea, anxiety and physical performance) prior to adding the latent variables into the structural equation model. All indicators were chosen based on the theoretical point of view. Maximum likelihood methods were used to estimate model parameters. Stata modification indices were examined to see whether the model fit is improved by removing or replacing specific measurement indicators. Structural equation modeling was then performed to test the hypotheses exploring the proposed relations among dyspnea, anxiety, depression, fatigue, and physical performance. Furthermore, subgroup analyses based on disease severity using lung function were conducted.

The model was assessed using multiple fit criteria: χ^2 goodness-of-fit statistic, the comparative fit index (CFI), the standardized root mean residual (SRMR), and the root mean square error of approximation (RMSEA). A statistically nonsignificant χ^2 ($p > .05$) is suggestive of a good match between the data and the hypothesized model. However, it has been shown that the chi-square test statistic would be significant for a big sample size. CFI, an incremental fit index measures how much a model being tested is improved compared to a baseline model. A high value of CFI is desirable. RMSEA, a parsimony-corrected index with its 90% confidence interval, measures lack of fit of a model. A value of zero RMSEA means the best fit. SRMR, a statistic related to the correlation residuals, measures the difference between the predicted and observed covariances. A low value of SRMR is desirable. Cutoff values to 0.95 for CFI, 0.05 for RMSEA, and 0.08 for SRMR were selected to indicate acceptable fit with a maximum likelihood estimation method (Kline, 2010).

Results

Participant Characteristics

A total of 302 COPD patients completed the baseline assessment. Among them, 282 patients wore Stepwatch during at least three days and they were included in the analyses (Table 2.1). It consisted of 80% males, with an average age of 68 years ($SD = 9$). Majority of the participants were White non-Hispanic (88%), and had at least a college degree (77%). Furthermore, more than half of them had an annual income of \$20,000 or more (61%), and were married or partnered (58%). Race/ethnicity and body mass index were significantly different between groups categorized by lung function (Table 2.1).

[Table 2.1 about here]

Means and standard deviations as original values before recoding for all measurements used in the SEM are presented in Table 2.2. Observed indicators of two constructs, Depression and Physical Performance were significantly different between groups by lung function. Bivariate correlations among 15 indicators used for five constructs are presented in Table 2.3.

[Table 2.2 and Table 2.3 about here]

CFA Results

A CFA was performed on covariance matrix of each indicator for constructs of dyspnea, anxiety, and physical performance which had at least three indicators. The initial CFA of dyspnea and anxiety fit the data well. The initial CFA of physical performance with five indicators including hand grip strength did not fit the data well. Hand grip strength was measured by a handgrip dynamometer to examine muscle strength of the upper extremities. The testing was repeated three times in the dominant hand while patients were in sitting position. The handgrip muscle strength was recorded in kilograms and the best value was taken for analysis. However, it had a large residual variance as 89.28 and R-squared as 0.03, and did not have a significant factor loading. Thus, the handgrip muscle strength measure was subsequently excluded from the SEM analyses.

The five-factor standard CFA showed an acceptable fit to the data, $\chi^2 (80) = 287.08$, $p < 0.001$; CFI = 0.92; SRMR = 0.08; RMSEA = 0.10. Stata modification indices indicated three sets of indicators having large modification indices: 6MWT and daily total step (41.11), HADS-A and PHQ-9 (22.93), and HADS-A and HADS-A (22.31). Therefore, correlated errors between these sets of indicators were added to the next CFA. The final fit of this model showed a better fit to the data, $\chi^2 (77) = 197.96$, $p < 0.001$; CFI = 0.95; SRMR = 0.07; RMSEA = 0.08 (Table 2.4).

[Table 2.4 about here]

SEM Results

The hypothesized model showed an acceptable fit to the data, $\chi^2 (77) = 197.96$, $p < 0.001$; CFI = 0.95; SRMR = 0.07; RMSEA = 0.08. A correlated error between constructs of Anxiety and Depression was added in the final model (Table 2.4). Overall, the specified predictors explained 56% of the variance in anxiety, 39% of the variance in depression, 68% of the variance in fatigue, and 81% of the variance in physical performance. The hypotheses about the paths were examined by SEM (Table 2.5).

[Table 2.5 about here]

Hypothesis 1 – Hypothesis 1 states that greater dyspnea is associated with greater anxiety, depression, and fatigue, and greater anxiety and depression are associated with greater fatigue. SEM results showed that increased levels of dyspnea was associated with increased levels of anxiety ($\beta = .472$, $p < .001$), depression ($\beta = .456$, $p < .001$), and fatigue ($\beta = .277$, $p < .001$). Furthermore, increased levels of anxiety ($\beta = .262$, $p < .01$) and depression ($\beta = .435$, $p < .001$) were associated with increased fatigue.

Hypothesis 2 – Hypothesis 2 states that greater dyspnea, anxiety, depression, and fatigue are associated with impaired physical performance. SEM results showed that increased level of dyspnea ($\beta = -.896$, $p < .001$) was related to impaired physical performance. On the other hand, higher level of anxiety was related to improved physical performance ($\beta = .266$, $p < .001$). There were no significant relationships between depression and fatigue with physical performance, but at least increased levels of both symptoms were related to impaired physical performance.

Hypothesis 3 – Hypothesis 3 states that dyspnea is indirectly associated with fatigue and impaired physical performance through anxiety and depression, and anxiety and depression are

indirectly associated with impaired physical performance through fatigue. SEM results showed that increased level of dyspnea ($\beta = .437, p < .001$) was indirectly related to only increased fatigue through anxiety and depression. Also, increased levels of anxiety ($\beta = -.244, p < .01$) and depression ($\beta = -.346, p < .001$) were indirectly related to impaired physical performance through fatigue.

Subgroup analyses by disease severity

Subgroup analyses by disease severity using FEV1 were presented in Figure 2 and 3. Different results from the final SEM model were as followed. Among patients with moderate lung function ($FEV1 \geq 50$ predicted), greater dyspnea was not related to greater fatigue ($\beta = .161, p = .119$), however, greater fatigue was related to impaired physical performance ($\beta = -.277, p < .05$). Among patients with severe lung function ($FEV1 < 50$ predicted), greater depressive symptoms were related to impaired physical performance ($\beta = -.291, p < .05$).

[Figure 2.2 and 2.3 about here]

Discussion

The aim of this study was to examine the direct effects of dyspnea, anxiety, depressive symptom, and fatigue on physical performance, as well as the indirect effect of these symptoms on physical performance by a SEM approach. Dyspnea was significantly associated with anxiety, depression, fatigue and impaired physical performance. Anxiety was significantly and positively associated with physical performance, while fatigue was insignificantly and negatively associated with physical performance. Dyspnea was indirectly associated with fatigue through anxiety and depressive symptoms, and anxiety and depressive symptoms were indirectly associated with impaired physical performance through fatigue.

The finding of the negative association between dyspnea and physical performance was consistent with previous studies (Blinderman et al., 2009; Esteban et al., 2010; Garcia-Aymerich et al., 2009). Dyspnea was the most disabling symptom affecting physical performance in current study. Increased levels of anxiety were positively associated with improved physical performance, showing the similar relationship from a previous finding with the same data of 148 COPD patients (Nguyen et al., 2013). This study suggested that increased daily steps may be a behavioral manifestation of the restlessness or as non-goal directed activities from high levels of anxious symptom (Nguyen et al., 2013). Although current analyses included both objective and subjective measurements for physical performance that are different from the previous study, the association between anxiety and physical performance was consistent. This finding should be cautiously interpreted, however, because greater anxious symptom cannot be treated as a reliable predictor of improved physical functioning for COPD patients. Higher anxiety is commonly considered as a demotivator of physical activity. Depressive symptom was not significantly associated with physical performance as supported by previous studies (Moy, Matthes, Stolzmann, Reilly, & Garshick, 2009; Watz, Waschki, Meyer, & Magnussen, 2009), while several other studies found significant association (Doyle et al., 2013; Spruit et al., 2010). These inconsistent findings could have been due to different assessment of depressive symptom or limited statistical power. The use of two commonly used measurements together (HADS-A and PHQ-9) for depressive symptom might provide more insight to understand the impact of this symptom.

Dyspnea was associated with fatigue as presented from previous studies (Doyle et al., 2013; Kapella et al., 2006). The finding of the significant relationship between dyspnea with fatigue and physical performance confirms that pulmonary rehabilitation recommended for

patients with dyspnea is beneficial to improve their symptoms and physical participation in daily activities (Global strategy for diagnosis, 2015). Furthermore, dyspnea was significantly associated with both anxiety and depressive symptoms that is consistent with previous findings (Di Marco et al., 2006; Janet Maurer et al., 2008). The indirect association between dyspnea and fatigue suggests partial mediating effects of psychological distress, and thus non-pharmacologic therapies including altered mood states would help COPD patients reduce fatigue symptom (Lacasse, Martin, Lasserson, & Goldstein, 2007).

Fatigue was significantly associated with all other symptoms as presented from previous studies (Baghai-Ravary et al., 2009; Doyle et al., 2013; Kapella et al., 2006). This strong association between dyspnea and fatigue has been supported by several studies, implying that shared underlying mechanisms are plausible for both pulmonary symptoms in COPD (Baghai-Ravary et al., 2009; Lewko, Bidgood, & Garrod, 2009). Thus, patients may not be able to differentiate two symptoms and often complain about them together (Stridsman et al., 2014). Anxiety and depressive symptoms are closely related with fatigue symptoms from previous studies (Doyle et al., 2013; Yohannes & Alexopoulos, 2014). The finding of the insignificant relationship of fatigue symptom with physical performance is inconsistent with previous studies (Altenburg et al., 2013; Baghai-Ravary et al., 2009; Kapella et al., 2006), while it shows at least the same direction. Prior studies showing the significant relationship used either a multi-dimensional measurement for fatigue (Multidimensional Fatigue Inventory (Lewko et al., 2009) or the Manchester COPD fatigue scale (Al-shair et al., 2009)) or a tool to measure the level of fatigue relating to performance status (Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FACIT-F (Al-shair et al., 2012)). Thus, one of the possible reasons for the insignificant association is that survey questions from SF36-V and CRQ-F do not directly ask

about the impact of fatigue symptom to their physical activity, but just ask single-dimensional level of tiredness of COPD patients.

Anxiety and depressive symptoms were examined separately because of different impacts on physical performance in previous findings (Nguyen et al., 2013). There were several published studies dealing with anxiety and depressive symptoms as one concept such as psychological distress (Holm, Bowler, Make, & Wamboldt, 2009; Yohannes & Alexopoulos, 2014), thus more studies are needed to analyze them separately. Furthermore, there is a conceptual difference on a construct of physical performance in this study. Daily total steps represent daily physical activity of patients, on the contrary 6MWT shows exercise capacity of COPD patients (Benton, 2014). Physical performance included both objective and subjective tools, and that has potential to induce different results from previous studies.

In my knowledge, there were limited numbers of path analyses had been conducted to examine similar relationships between symptoms and physical performance in COPD patients (Altenburg et al., 2013; Kapella et al., 2006). However, they did not use multiple indicators for a construct (Kapella et al., 2006) and treated fatigue and 6MWT together for a construct of functional capacity (Altenburg et al., 2013). Therefore, this would be the first attempt to conduct SEM approach to examine the relationships between symptoms and physical performance in COPD. The similar relationships among several symptoms have been explored by SEM approach in other chronic illness such as multiple sclerosis (Amtmann et al., 2015) and rheumatoid arthritis (Nicassio et al., 2012).

There are some limitations of this study. First of all, the analyses were based on cross-sectional design. We cannot determine which symptom comes first because of the cross-sectional nature of the analyses. Reciprocal associations between four symptoms and physical

performance is plausible. Longitudinal studies are needed to examine the directionality and causality for these complex relationships. Second, there were only 20% female participated in the study, which makes it difficult to conduct subgroup analysis by gender. It has been reported that women have more symptoms and lower physical capacity than men in COPD, although the underlying mechanisms are not clear yet (Han et al., 2007; Todt et al., 2014). Third, three individual questions were used to measure anxiety symptom in order to have at least two indicators for a construct of anxiety. Although these single items had significant factor loadings, they may not allow comprehensive evaluations of anxiety compared to a composite measure. Fourth, symptoms of sleep disorder and pain were not included as common symptoms of COPD in the hypothesized model. Recent studies showed that some of COPD patients experience thoracic pain, insomnia and obstructive sleep apnea (Budhiraja, Siddiqi, & Quan, 2015; Janssen, Wouters, Parra, Stakenborg, & Franssen, 2016). Further research are needed to examine the impact of sleep disturbance and pain in relation with other symptoms, and their effects on physical functioning.

Conclusions

The results of this cross-sectional analyses showed that dyspnea, anxiety and depression had direct effects on fatigue as well as dyspnea and anxiety had direct effects on physical performance for COPD patients. Dyspnea was the strongest contributor among major symptoms for physical performance in COPD. Longitudinal studies are needed to confirm the directionality of these relationships between symptoms and physical performance. It can provide insight for the physical and psychological intervention as symptom management to improve physical performance for COPD population.

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Table 2.1
Demographic and Clinical Characteristics

	Total Sample (n = 282)	Severe COPD (n = 170)	Moderate COPD (n = 112)	<i>p</i> -value
	Mean ± SD or n (%)			
Socio-Demographics				
Age, years	67.7 ± 8.6	67.2 ± 8.1	68.6 ± 9.3	.175
Gender, women	56 (19.9)	32 (18.8)	24 (21.4)	.592
Race/Ethnicity				
Caucasians	249 (88.3)	106 (94.6)	143 (84.1)	
African-American	18 (6.4)	15 (8.8)	3 (2.7)	
Native Americans/Alaskan Native	8 (2.8)	7 (4.1)	1 (0.9)	.039
Asian	3 (1.1)	2 (1.2)	0	
Other	4 (1.4)	3 (1.8)	1 (0.9)	
Education				
High school or less	64 (22.7)	42 (24.7)	22 (19.6)	
Some college or more	218 (77.3)	128 (75.3)	90 (80.4)	.321
Income (n = 279)				
< 20K/year	108 (38.7)	70 (41.4)	38 (34.5)	
≥ 20K/year	171 (61.3)	99 (58.6)	72 (65.5)	.249
Marital status				
Partnered	163 (57.8)	100 (58.8)	63 (56.3)	
Un-partnered	119 (42.2)	70 (41.2)	49 (43.7)	.669
Body Mass Index	28.2 ± 6.2	27.6 ± 6.7	29.1 ± 5.3	.042
Current smoker	76 (27.0)	42 (24.7)	34 (30.4)	.295
Disease Severity				
FEV1/FVC	0.45 ± 0.12	0.39 ± 0.11	0.54 ± 0.09	< .001
FEV1 % predicted	44.9 ± 15.8	34.3 ± 9.5	61.1 ± 7.4	< .001

Note. FEV1 = the forced expiratory volume in one second; FVC = the forced vital capacity.

Table 2.2
Mean Scores of Observed Variables

	Total Sample (n = 282)	Severe COPD (n = 170)	Moderate COPD (n = 112)
<i>Dyspnea</i>			
1 CRQ-D***	23.83 ± 6.74	21.84 ± 6.46	26.84 ± 6.01
2 UCSD-SOB***	42.86 ± 22.34	49.46 ± 21.43	32.85 ± 19.90
3 mMRC***	1.94 ± 1.08	2.17 ± 1.07	1.60 ± 1.01
<i>Anxiety</i>			
4 HADS-A	5.05 ± 3.95	4.83 ± 3.74	5.38 ± 4.24
5 SF36-MH1	2.29 ± 1.37	2.24 ± 1.33	2.37 ± 1.43
6 CRQ-EF4	3.90 ± 1.71	3.91 ± 1.72	3.89 ± 1.71
7 CRQ-EF7	3.16 ± 1.52	3.15 ± 1.55	3.18 ± 1.48
<i>Depression</i>			
8 HADS-D	4.23 ± 4.13	4.28 ± 3.93	4.15 ± 4.43
9 PHQ-9	6.16 ± 4.75	6.09 ± 4.73	6.28 ± 4.81
<i>Fatigue</i>			
10 SF36-V	46.6 ± 12.39	46.35 ± 12.51	47.05 ± 12.26
11 CRQ-F	15.80 ± 4.88	15.72 ± 4.82	15.92 ± 4.98
<i>Physical Performance</i>			
12 6MWT***	1091 ± 372	1012 ± 376	1211 ± 334
13 Daily Total Steps**	6002 ± 3343	5461 ± 3145	6823 ± 3479
14 SF36-RP*	29.17 ± 36.93	25.44 ± 35.20	34.82 ± 38.90
15 SF36-PF***	39.38 ± 22.52	33.76 ± 20.36	47.90 ± 23.05

Note. * $p < .05$. ** $p < .01$. *** $p < .001$.

CRQ-D = Chronic Respiratory Questionnaire - Dyspnea subscale; UCSD-SOB = University of California, San Diego Shortness of Breath Questionnaire; mMRC = the modified Medical Research Council dyspnea score; HADS-A = the Hospital Anxiety and Depression Scale - Anxiety; SF36-MH1 = the Medical Outcomes Study Short Form-36 - Mental Health subscale question 1; CRQ-EF4 = Chronic Respiratory Questionnaire - Emotional Function subscale question 4; CRQ-EF7 = Chronic Respiratory Questionnaire - Emotional Function subscale question 7; HADS-D = the Hospital Anxiety and Depression Scale - Depression; PHQ-9 = the Patient Health Questionnaire-9; SF36-V = the Medical Outcomes Study Short Form-36 - Vitality subscale; CRQ-F = Chronic Respiratory Questionnaire - Fatigue subscale; 6MWT = the six minute walk test; SF36-RP = the Medical Outcomes Study Short Form-36 - Role Physical subscale; SF36-PF = the Medical Outcomes Study Short Form-36 - Physical Functioning subscale.

Table 2.3
Correlations among Observed Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Dyspnea															
1 CRQ-D	1.00														
2 UCSD-SOB	.83***	1.00													
3 mMRC	.55***	.60***	1.00												
Anxiety															
4 HADS-A	.37***	.23***	.07	1.00											
5 SF36-MH1	.32***	.25***	.08	.52***	1.00										
6 CRQ-EF4	.44***	.32***	.16**	.55***	.51***	1.00									
7 CRQ-EF7	.45***	.35***	.14*	.64***	.52***	.70***	1.00								
Depression															
8 HADS-D	.35***	.29***	.18**	.63***	.38***	.53***	.50***	1.00							
9 PHQ-9	.43***	.36***	.21**	.63***	.40***	.58***	.63***	.73***	1.00						
Fatigue															
10 SF36-V	.37***	.40***	.26***	.21**	.18**	.41***	.40***	.39***	.40***	1.00					
11 CRQ-F	.53***	.48***	.26***	.41***	.34***	.56***	.60***	.51***	.63***	.60***	1.00				
Physical Performance															
12 6MWT	-.41***	-.44***	-.45***	.03	-.04	-.05	-.02	-.11	-.10	-.15*	-.18**	1.00			
13 Daily Total Steps	-.32***	-.37***	-.42***	.13*	.03	.00	.01	-.09	-.09	-.20**	-.14*	.55***	1.00		
14 SF36-RP	-.54***	-.49***	-.34***	-.24***	-.25***	-.34***	-.33***	-.35***	-.38***	-.34***	-.52***	.26***	.29***	1.00	
15 SF36-PF	-.72***	-.78***	-.61***	-.14*	-.22**	-.28***	-.25***	-.28***	-.31***	-.42***	-.43***	.52***	.48***	.58***	1.00

Note. CRQ-D = Chronic Respiratory Questionnaire - Dyspnea subscale; UCSD-SOB = University of California, San Diego Shortness of Breath Questionnaire; mMRC = the modified Medical Research Council dyspnea score; HADS-A = the Hospital Anxiety and Depression Scale - Anxiety; SF36-MH1 = the Medical Outcomes Study Short Form-36 - Mental Health subscale question 1; CRQ-EF4 = Chronic Respiratory Questionnaire - Emotional Function subscale question 4; CRQ-EF7 = Chronic Respiratory Questionnaire - Emotional Function subscale question 7; HADS-D = the Hospital Anxiety and Depression Scale - Depression; PHQ-9 = the Patient Health Questionnaire-9; SF36-V = the Medical Outcomes Study Short Form-36 - Vitality subscale; CRQ-F = Chronic Respiratory Questionnaire - Fatigue subscale; 6MWT = the six minute walk test; SF36-RP = the Medical Outcomes Study Short Form-36 - Role Physical subscale; SF36-PF = the Medical Outcomes Study Short Form-36 - Physical Functioning subscale.

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 2.4
Model Fit Indexes

	χ^2_M	df _M	RMSEA	CFI	SRMR
Measurement model					
5-factor standard CFA	287.077 ^a	80	.096	.917	.077
5-factor CFA with three correlated errors ^b	197.961 ^a	77	.075	.952	.070
Structural regression model					
Hypothesized model ^c	197.961 ^a	77	.075	.952	.070

^a $p < .001$; ^b allowing three correlated errors between six minute walk test and daily total steps, HADS-A and HADS-D, and HADS-A and PHQ-9; ^c allowing four correlated errors between Anxiety and Depression, six minute walk test and daily total steps, HADS-A and HADS-D, and HADS-A and PHQ-9.

Note. RMSEA, root mean square error of approximation; CFI, comparative fit index; SRMR, standardized root mean residual.

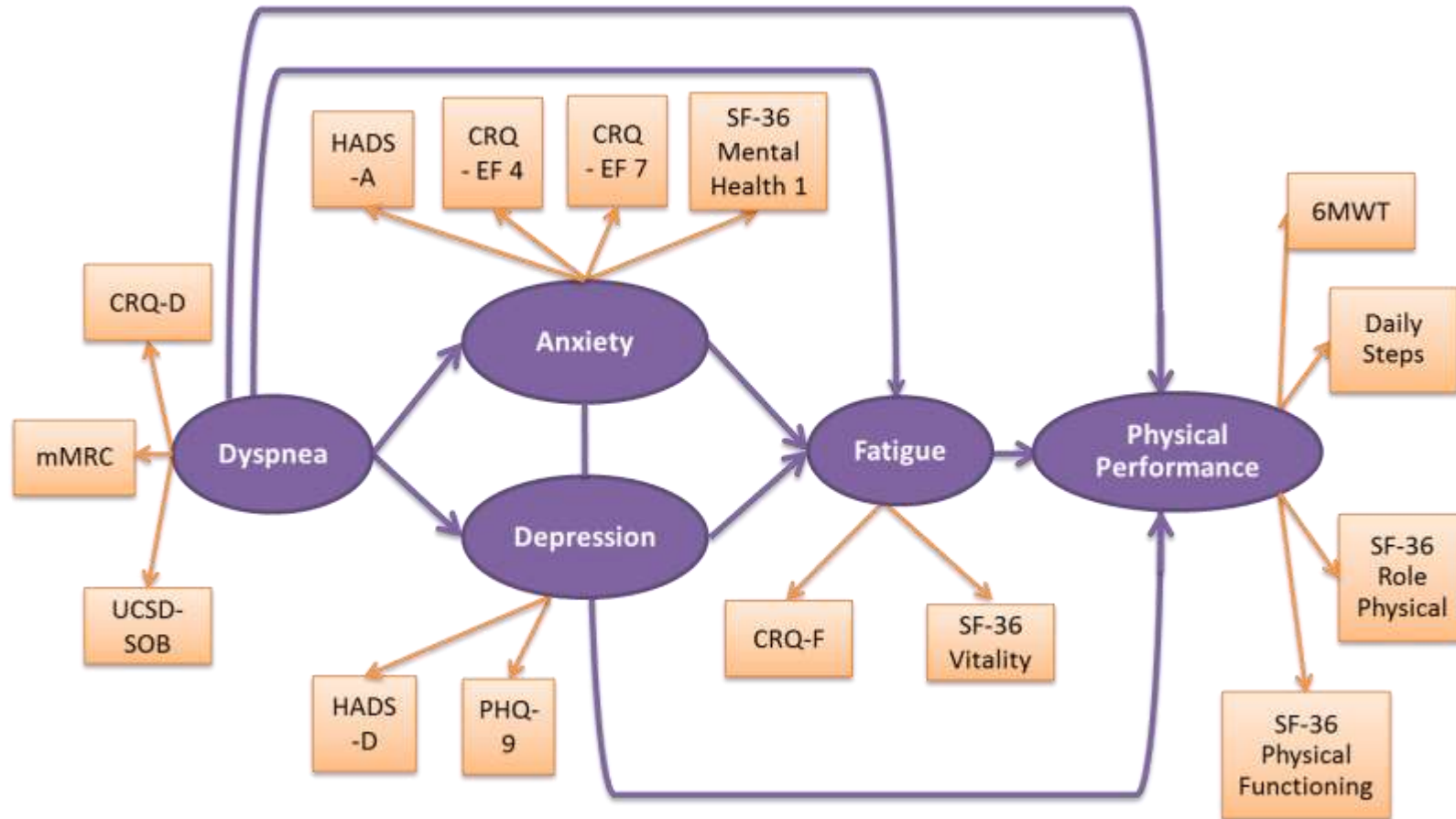
Table 2.5
 Path Coefficients from Final Structural Equation Model

	Unstandardized	SE	Standardized
Direct effects			
Dyspnea -> Anxiety	0.222***	.032	.472***
Dyspnea -> Depression	0.251***	.035	.456***
Dyspnea -> Fatigue	0.376***	.082	.277***
Anxiety -> Fatigue	0.755**	.247	.262**
Depression -> Fatigue	1.073***	.210	.435***
Dyspnea -> Physical Performance	-3.155***	.209	-.896***
Anxiety -> Physical Performance	1.994***	.543	.266***
Depression -> Physical Performance	-.591	.468	-.092
Fatigue -> Physical Performance	-.323	.235	-.124
Indirect effects			
Dyspnea -> Fatigue	0.437***	.071	-
Dyspnea -> Physical Performance	0.032	.130	-
Anxiety -> Physical Performance	-0.244**	.080	-
Depression -> Physical Performance	-0.346***	.068	-

Note. ** $p < .01$. *** $p < .001$.

Figure 2.1

Hypothesized Model of the Effect of Symptoms on Physical Performance in COPD



Note. CRQ-D = Chronic Respiratory Questionnaire - Dyspnea subscale; mMRC = the modified Medical Research Council dyspnea score; UCSD-SOB = University of California, San Diego Shortness of Breath Questionnaire; HADS-A = the Hospital Anxiety and Depression Scale - Anxiety; CRQ-EF4 = Chronic Respiratory Questionnaire - Emotional Function subscale question 4; CRQ-EF7 = Chronic Respiratory Questionnaire - Emotional Function subscale question 7; SF36-MH1 = the Medical Outcomes Study Short Form-36 - Mental Health subscale question 1; HADS-D = the Hospital Anxiety and Depression Scale - Depression; PHQ-9 = the Patient Health Questionnaire-9; CRQ-F = Chronic Respiratory Questionnaire - Fatigue subscale; SF36-V = the Medical Outcomes Study Short Form-36 - Vitality subscale; 6MWT = the six minute walk test; SF36-RP = the Medical Outcomes Study Short Form-36 - Role Physical subscale; SF36-PF = the Medical Outcomes Study Short Form-36 - Physical Functioning subscale.

Figure 2.2

Effects of Symptoms on Physical Performance among Patients with Moderate COPD

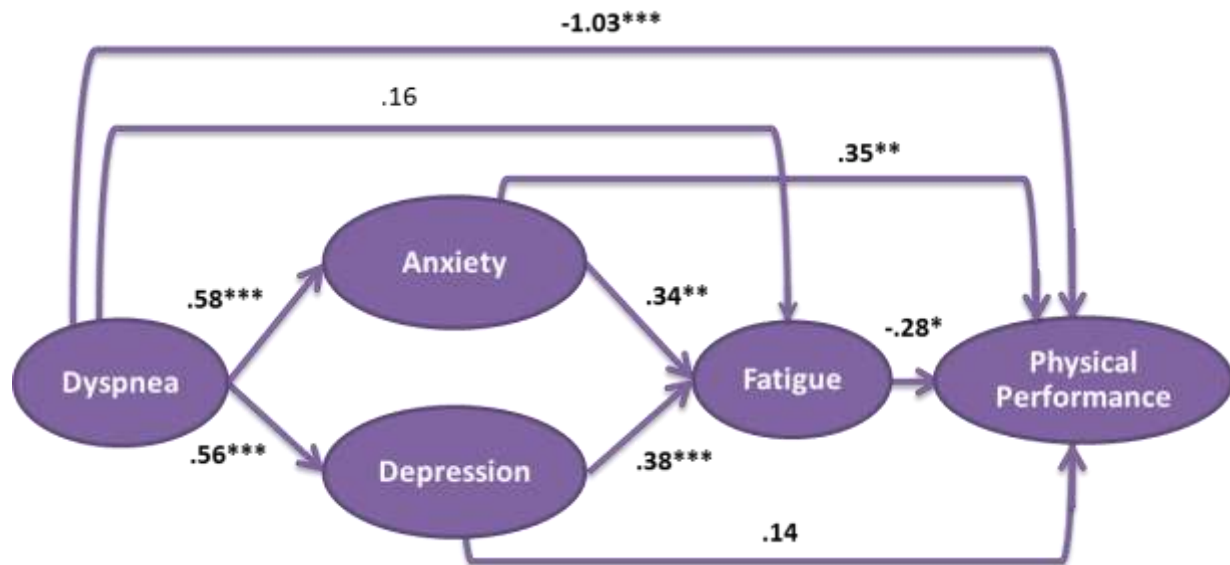
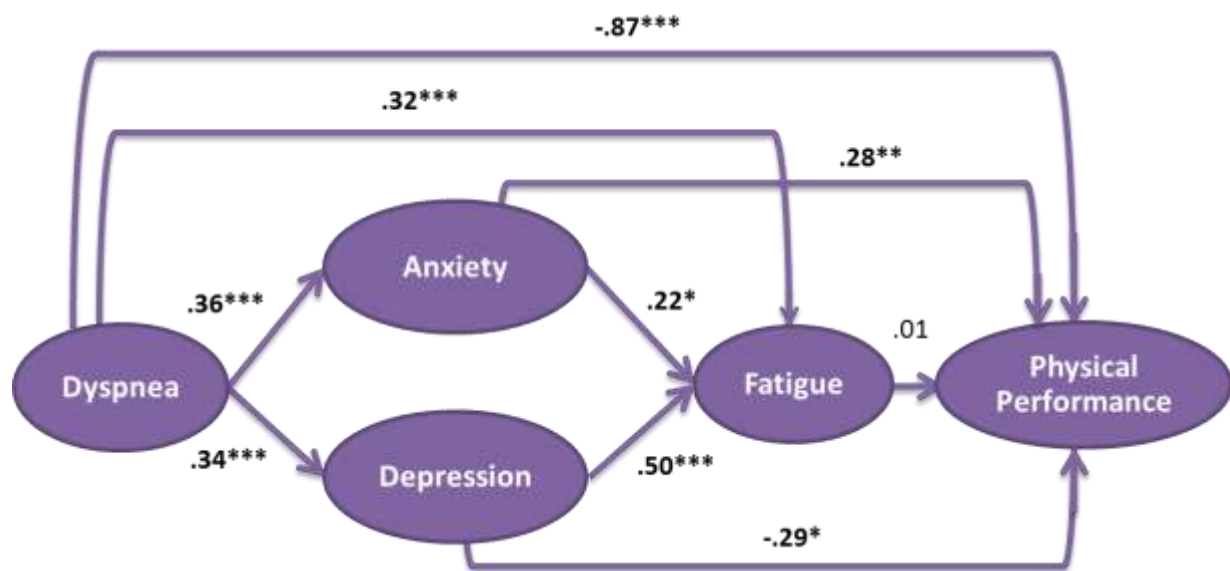


Figure 2.3

Effects of Symptoms on Physical Performance among Patients with Severe COPD



Chapter 3

Inflammation and Fatigue in Patients with COPD

Abstract

Background: Fatigue is a prevalent symptom in chronic obstructive pulmonary disease (COPD). It is increasingly considered to be a key symptom and important clinical indicator of physical inactivity and exacerbation frequency. Although recent studies in neuroimmunology suggests that inflammation may play a role in development of fatigue, the underlying mechanism of COPD-related fatigue is still unknown. **Aim:** The purpose of this study was to examine an association between inflammation markers and fatigue symptom over one year in COPD patients. **Methods:** This study is part of a longitudinal observational study of COPD patients to examine the biological causes and functional consequences of depression. The data used in the study were collected at baseline and after one year. Systemic inflammation markers included C-reactive protein (CRP) and pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor - α (TNF- α). Fatigue was measured by the Fatigue subscale of the Chronic Respiratory Questionnaire (CRQ) and the Vitality subscale of the 36-item Short Form Health Survey (SF-36). Potential confounders included age, gender, smoking status, disease severity, and symptoms of depression and anxiety. Multivariate hierarchical linear regression analyses and were conducted using longitudinal dataset. **Results:** A total of 234 COPD patients consisted of 80% males, with an average age of 68 years. Modest correlations were found between two systemic inflammatory markers (IL-8 and CRP) and fatigue (CRQ). These two markers were still associated significantly with fatigue score after adjusting for confounders in multivariate

analyses. Depressive symptom is closely associated with fatigue symptom over one year.

Conclusions: The findings of this study indicated that CRP may serve as a potential biomarker of fatigue symptom in COPD.

Keywords: C-reactive protein, inflammation, fatigue, depression, COPD

Introduction

Fatigue is the second most prevalent symptom after dyspnea in patients with chronic obstructive pulmonary disease (COPD) with a prevalence as high as 71% among COPD patients (Park, Meldrum, & Larson, 2013; Walke et al., 2007). It is a prominent disease-related symptom from the patient's perspective that adversely affects activities of daily living (Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009). In COPD, fatigue is increasingly considered to be a key symptom and important clinical indicator of physical inactivity and exacerbation frequency (Baghai-Ravary et al., 2009; Park & Larson, 2014; Stridsman, Lindberg, & Skar, 2014). The underlying mechanism of fatigue is still unknown and thus effective management of fatigue is difficult (Lewko, Bidgood, & Garrod, 2009). Recent studies suggest that there are multiple influencing factors including physiological, sociodemographic, and psychological factors for fatigue symptom in COPD (Karakurt & Unsal, 2013; Paddison, Effing, Quinn, & Frith, 2013). These include age, gender, race, marital status, airway obstruction, physical capacity, and symptoms of depression, anxiety, or sleep disturbance. Given that COPD is a complex disease with various health outcomes, a multidimensional index including multiple factors would be a better predictor of fatigue symptom than a single factor alone (Kelly, Owen, Pinto-Plata, & Celli, 2013). Among physiological factors, the relationship between traditional disease severity of COPD as airflow obstruction and fatigue symptom is still unclear in several studies (Antoniou & Ungureanu, 2015; Eckerblad et al., 2014; Todt et al., 2014). It has been suggested that disease-related fatigue symptom may be explained by activation of immune-inflammatory pathways (Dantzer, Heijnen, Kavelaars, Laye, & Capuron, 2014).

COPD is characterized by chronic inflammation in airways, parenchyma, and pulmonary vasculature (Global strategy for the diagnosis). Persistent, low-level, systemic inflammation is

observed in some of COPD patients (Agusti et al., 2012; Agusti & Sin, 2014; Barnes, 2009; Global strategy for the diagnosis). Multiple cytokines play a key role in developing chronic inflammation and more than 50 cytokines have been identified as inflammatory markers in COPD (Al-shair et al., 2011; Barnes, 2009; Gan, Man, Senthilselvan, & Sin, 2004). Several systemic inflammatory markers such as C-reactive protein (CRP), fibrinogen, leucocytes, and tumor necrosis factor- α (TNF- α) were significantly increased among individuals with COPD compared to healthy control groups (Gan et al., 2004). Cytokines function in complex networks and each role of the complex interactions are still unclear (Barnes, 2009). Pro-inflammatory cytokines such as interleukin-6 (IL-6) and TNF- α develop the inflammatory response (Kelley et al., 2003). They may be involved in the pathological pathways resulting in airflow limitation (Barnes, 2009). Both cytokines are increased in the sputum of COPD patients, especially during exacerbations (Agusti & Sin, 2014). IL-6 stimulates CRP release from the liver and thus is positively related with increased level of CRP. It connects innate and acquired immunity by working together with other cytokines (MacNee, 2013). CRP has been found to be associated with other inflammatory markers including IL-6 and IL-8, and the level is higher in stable COPD patients compared to healthy population (Barnes, 2009; MacNee, 2013). CRP may act as an indication of persistent state of inflammation (Pepys & Hirschfield, 2003). IL-8 was the first identified chemokine in COPD. It is significantly increased in sputum of COPD patients and positively correlated with increased neutrophils (Barnes, 2009).

Recent studies suggested that proinflammatory cytokines act in the brain to induce sickness behaviors including depression and fatigue (Al-shair et al., 2011; Dantzer & Kelley, 2007; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Systemic inflammation is also associated with impaired lung function, impaired physical functioning, mortality, COPD

exacerbations, and extrapulmonary comorbid conditions (Gan et al., 2004; Lu et al., 2013; MacNee, 2013; Man et al., 2006; Sethi et al., 2012). Researchers found that elevated level of proinflammatory cytokines is associated with fatigue symptom in healthy population as well as in ill patients including cancer, multiple sclerosis, viral infections, mood disorders, and neurologic disease (Al-shair et al., 2011; Bower et al., 2011; Dantzer et al., 2014; Lasselin et al., 2012). However, whether systemic inflammation is related to fatigue symptom is controversial (Al-shair et al., 2011; Dantzer et al., 2008; Gan et al., 2004; Lewko et al., 2009). Examining these potential relationships is needed to understand the pathophysiologic mechanism involved in COPD-related fatigue symptom. Since most studies regarding this relationship were cross-sectional, longitudinal data analyses are needed to better understand the mechanism of fatigue in COPD.

The aim of this research is to examine an association between inflammation markers and fatigue symptom over one year in COPD patients.

Methods

Design

This study is part of a longitudinal observational study of COPD patients to examine the biological causes and functional consequences of depression. The data used in this study were collected in the baseline phase and after one year. Informed consent was obtained from all participants, and the study was approved by the institutional review boards at three clinical sites.

Procedure

Participants were recruited from numerous sources. These included outpatient clinics from the three medical centers, pulmonary rehabilitation programs, a research database maintained by the investigators, queries of medical records and pulmonary function tests, Better

Breathers Club, community pulmonary practices, advertisements, study website, and other referrals. Baseline study assessments were conducted both in person and by telephone. Clinic visit included a blood draw, spirometry testing, six minute walk test, and completion of symptom-based questionnaires. Telephone contact with a trained mental health professional was scheduled two days after the in-person visit and included assessment of psychological distress. The same procedure was repeated at after one year follow-up.

Eligibility

The inclusion criteria for this study were: 1) Diagnosis of COPD confirmed by the following: 1-a) post-bronchodilator Forced Expiratory Volume in one second to Forced Vital Capacity ratio (FEV1/FVC) < 70%; 1-b) moderate to very severe disease by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (FEV1 < 80%), 2) Age \geq 40 years, 3) A history of current or past cigarette smoking (> 10 pack-years), 4) Stable disease with no acute exacerbations in the past 4 weeks, and 5) Ability to speak, read and write English. Patients with any of the following conditions were excluded: other chronic obstructive lung diseases (e.g., asthma, bronchiectasis and cystic fibrosis), idiopathic pulmonary fibrosis, primary pulmonary vascular disease, uncompensated congestive heart failure, non-COPD-related chronic inflammatory diseases, infectious disease or auto-immune disease, HIV/AIDS, lung cancer or metastatic cancer, chronic renal failure, chronic uncompensated liver disease, chronic antibiotic use or ongoing infection, chronic oral prednisone use, and psychologic disease (e.g., bipolar disease, psychotic disorders, and dementia).

Measures

Inflammatory markers. Systemic inflammation markers include high sensitivity CRP and a panel of pro-inflammatory cytokines of IL-6, IL-8, and TNF- α . After the spirometer test

venous blood samples were obtained in a vacutainer with an anticoagulant (ethylenediaminetetraacetic acid [EDTA]). The plasma was obtained by centrifugation of whole blood at 2000 g (3400 RPM) for 10 minutes. Samples were stored at -70°C freezer prior to analysis. The CRP concentrations were measured by a duoset ELISA (R&D Systems Inc. Minneapolis, MN 55413) and the lower limit of detection was 15.5 pg/mL. The concentrations of IL-6, IL-8, and TNF- α were measured by a Luminex multiplex platform with Millipore Milliplex High Sensitivity Human Cytokine Magnetic Beads (EMD Millipore Corporation, Darmstadt, Germany). The lower limit of detection of cytokines was 0.13 pg/mL.

Fatigue. Fatigue symptom was measured by two instruments: the fatigue subscale of the Chronic Respiratory Questionnaire (CRQ) (Guyatt, Berman, Townsend, Pugsley, & Chambers, 1987) and the Vitality subscale of the 36-item Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992). The CRQ is a disease-specific quality of life questionnaire for patients with COPD. The fatigue subscale of CRQ is a 4-item scale with a range of 1 (*extremely fatigue*) to 7 (*not at all fatigue*). Scores may range from 1 to 7, higher scores representing less severe fatigue. The SF-36 is one of the most frequently used measures of quality of life in various groups. The Vitality subscale is a 4-item subscale with a range of 1 (*all of the time*) to 6 (*none of the time*). Scores may range from 0 to 100, higher scores indicating higher level of vitality. Numerous published studies showed reliability and validity of both tools. In this study, internal consistency estimated using Cronbach's alpha was .88 for CRQ and .85 for SF-36.

Potential confounders. Potential biobehavioral confounders were added in the multivariate analyses. Demographic variables included age, gender, and ethnicity (white or non-white). Health-related behavior included smoking status in the past week (yes or no). Disease severity included a multidimensional measure (BODE Index) that was calculated by a summary

score of **B**ody mass index (BMI), airway **O**bstruction (predicted amount as a percentage of the forced expiratory lung volume in one second), **D**yspnea (modified medical research council dyspnea scale; mMRC), and **E**xercise (six minute walking distance) (Celli et al., 2004). It ranges from 0 to 10, higher scores indicating higher risk of death. Fatigue-related symptoms included symptoms of depression and anxiety measured by the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). HADS is a valid and reliable 14-item measure of psychological distress. Scores for each subscale of anxiety and depression symptom may range from 0 to 21, higher scores indicating higher level of psychological stress.

Statistical Analyses

Data analyses were conducted using Stata 14.0 (StataCorp LP, College Station, Texas) with the significance level set at $\alpha = 0.05$. Two fatigue symptom scores (SF36-V and CRQ-F) and four inflammatory makers (IL-6, IL-8, TNF-a, and CRP) were analyzed as continuous variables. The values of four inflammatory markers were log-transformed because of the skewed distribution of them. For exploratory analyses, cut off of values greater than the 75th percentile was used to indicate high levels of inflammation, except cut off of 3 mg/L for CRP. Continuous variables were expressed as mean \pm SD and categorical variables were shown as frequencies. Student t-test was used to assess significance of the differences between subgroups by covariates. Covariates included demographics (age, gender) and clinical variables (smoking status, BODE index, and symptoms of depression and anxiety). In order to describe the change of fatigue symptom and inflammatory markers over one year, the slopes of change over time for each variable were calculated, and these were used in univariate and multivariate analyses.

First, univariate correlation analyses were performed to examine the cross-sectional associations between inflammatory makers and fatigue symptom at baseline. The same analyses

were repeated with slopes of inflammatory makers and fatigue symptom over one year. Second, multivariate linear regression analysis was performed to examine the cross-sectional associations between inflammatory makers and fatigue symptom at baseline. The regression model was adjusted for selected covariates. Third, the hierarchical linear regression was performed to determine significant predictors of the slope of fatigue symptom. The independent variables were entered into the regression model, with step 1 forced entry of age, gender, smoking status and baseline fatigue score; step 2 forced entry of BODE index; step 3 forced entry of symptoms of depression and anxiety; and step 4 forced entry of IL-6, IL-8, TNF-a, and CRP. Variables that are not easily modifiable with interventions were entered first. Regression diagnostic checks for normality, homoscedasticity, and multicollinearity were performed.

Results

Participant Characteristics

A total of 234 COPD patients who completed all the surveys and the blood test at baseline as well as after one-year follow-up visit was included in this study. Subjects' characteristics and baseline values are presented in Tables 3.1 and 3.2. It consisted of 80% males, with an average age of 68 years (SD = 9). There were 47 (20%) at new GOLD class A, 31 (13%) at class B, 56 (24%) at class C, and 100 (43%) at class D.

[Table 3.1 and 3.2 about here]

Changes of Inflammation Markers and Fatigue Symptom

At baseline, patients reported moderate levels of fatigue measured by two measurements (Table 3.2). There were no significant differences of fatigue symptom between the groups based on gender, marital status, or smoking status. After one year, scores of fatigue symptom did not change significantly (Table 3.2). The original values of four inflammatory markers are shown in

Table 3.2. The levels of all four cytokines increased after one year, however the change in CRP levels was not significant. There were mild to moderate correlations between four inflammatory markers as shown in Table 3.3, however, the degree of associations changed smaller after one year.

[Table 3.3 about here]

Univariate analyses

At baseline, the systemic inflammatory markers showed weak associations with fatigue symptom (Table 3.3). IL-8 and CRP were associated with CRQ-F, and IL-8 and TNF- α with SF36-V. CRP had a negative correlation with fatigue score, showing higher level of CRP was associated with worse fatigue. For exploratory analyses, the cut-off point as 75th percentile for IL-6, IL-8, and TNF- α , and 3 mg/L for CRP were selected to categorize the participants into high or low inflammation group. Among them, Figure 3.1 shows the significant result that patients with higher CRP levels had lower mean CRQ-F score than those with lower CRP level (3.8 vs 4.2, $p < .01$).

[Figure 3.1 about here]

The slope of change in fatigue symptom was not associated with baseline values of four inflammation markers. The slope of CRQ-F was negatively associated with the slope of IL-6 (Table 3.4). The slope of fatigue symptom was correlated with the slopes of both depression ($r = -.30, p < .001$) and anxiety symptoms ($r = -.14, p < .05$), but was not correlated with the slope of BODE index ($r = -.11, p = .08$) over one year.

[Table 3.4 about here]

Multivariate analyses

[Table 3.5 about here]

The multivariate regression model for fatigue symptom based on baseline data is presented in Table 3.5. There were significant cross-sectional associations between two inflammatory markers (IL-8 and CRP) and fatigue symptom (both CRQ-F and SF36-V) in the unadjusted multivariate model. After adjustment for age, gender, smoking status, BODE index, symptoms of depression and anxiety, the associations remained significant with only CRQ-F (adjusted $\beta = 0.18$ for IL-8, $p < 0.05$; adjusted $\beta = -0.16$ for CRP, $p < 0.05$). In practical terms, $\beta = -0.16$ means that, for a 10% increase in CRP level, there would be a decrease of 0.02 in the CRQ-F score. The adjusted multivariate model using CRQ-F showed significant relationships between symptoms of anxiety (adjusted $\beta = -0.16$, $p < 0.05$) and depression (adjusted $\beta = -0.34$, $p < 0.001$) with fatigue. The model explained 27.6% of the variance in fatigue symptom at baseline.

[Table 3.6 about here]

The hierarchical regression model for the change of fatigue symptom (CRQ-F) after one year is presented in Table 3.6. Age, gender, smoking, and baseline CRQ-F score accounted for 13% of the variance in the slope of fatigue symptom. The addition of BODE index and depressive and anxious symptoms accounted for an additional 5% of the variance in the slope of fatigue symptom. The final model explained approximately 19% of the variance in the slope of fatigue symptom, and the primary predictor was the slope of depressive symptom (adjusted $\beta = -0.26$, $p < 0.001$). There was no significant relationship between the slopes of four inflammatory cytokines and fatigue symptom over one year. For exploratory analyses, multilevel linear regression was performed while time is treating as a categorical variable (baseline as 0 and follow-up after one year as 1). Interaction terms were included between inflammation markers

and time in order to examine the effect of inflammation on change in fatigue score over one year. However, there was no significant result from any independent variables for fatigue symptom.

Discussion

The aim of this study was to explore the association between systemic inflammation and fatigue using four inflammatory cytokines and two fatigue scales over one year in patients with moderate to severe COPD. There were modest correlations between two systemic inflammatory markers and fatigue. These two markers (IL-8 and CRP) were still associated significantly with CFQ-F score after adjusting for covariates in multivariate analyses. However, in the longitudinal data analyses using slopes of change over one year as well as multilevel models did not show any significant associations between systemic inflammation and fatigue.

Fatigue symptom score did not change significantly, however it was minimally improved after one year. In a recent longitudinal study, they reported a similar trend on fatigue score over three years in COPD patients (Cho, Kivimaki, Bower, & Irwin, 2013). Interestingly, FEV1 did not change (45.6 to 46.2, $p = 0.30$). On the contrary, dyspnea symptom was insignificantly impaired as mMRC showed a non-significant change from 1.88 to 1.94 and UCSD-SOB changed from 42 to 44. These minor changes showed that participants were experiencing stable symptoms over a year. In this study we used strict inclusion criteria by excluding patients with other chronic diseases. Moreover, 19% of participants did not complete the clinic visit including a blood draw after one year, indicating the possibility of worsening symptoms or increased disease severity for whom dropped out. Further studies with longer periods of follow-up are needed to understand better about changes for disease severity and symptom experiences of COPD patients.

Our levels of inflammatory cytokines were similar to a large cohort study with 1,755 COPD patients (Agusti et al., 2012). Insignificant associations between IL-6 and fatigue was inconsistent with previous studies (Bossola, Di Stasio, Giungi, Rosa, & Tazza, 2015; de Raaf et al., 2012). Our study measured fatigue symptoms only uni-dimensionally. In a recent study measured fatigue multi-dimensionally among cancer patients, IL-6 was associated with physical fatigue but not with mental fatigue (de Raaf et al., 2012). Findings from an earlier review showed significantly positive correlations between cancer-related fatigue and IL-6, but not with TNF-a (Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). CRP was significantly related with fatigue symptom in this study from both univariate and adjusted multivariate analyses. In a recent study, fatigue symptom had a weak correlation with CRP ($r = 0.19$, $p = 0.05$) as well as TNF-a ($r = 0.24$, $p = 0.01$) among moderate COPD patients (Al-shair et al., 2011). In a study with breast cancer survivors, fatigue symptom was significantly associated with CRP ($\beta = 0.12$, $p = 0.02$) (Orre et al., 2011). Population-based evidence showed that CRP and IL-6 were prospectively associated with fatigue measured by SF-36 Vitality, and higher levels of both biomarkers predicted fatigue symptom after three years (Cho et al., 2013). The significant relationship between CRP and fatigue implies that fatigue symptom may be related to persistent inflammation (Cho et al., 2013; Pepys & Hirschfield, 2003).

Statistically significant relationship between IL-8 and fatigue symptom did not seem to be clinically significant since it has been known that increased level of IL-8 are related to impaired symptoms. IL-8 is a chemokine and a major mediator of inflammatory response. Researchers recently reported that the relationship between IL-8 and SF36-V in COPD patients with a six minute walk test of less than 350 meters (0.22 miles) was highly significant ($r = -0.74$, $p = 0.01$), which shows an opposite direction of relationship from the current study (Kohli et al.,

2015). They included several cytokines such as IL-6, CRP, Fibrinogen, and TNF- α , and only IL-8 was significantly related to nonphysical domains. When we performed the similar approach to their analyses (Kohli et al., 2015), there was no significant relationship between IL-8 and fatigue measured by SF36-V ($r = -0.02$, $p = 0.85$). Furthermore, similar relationships were found in a study with patients with non-small cell lung cancer, showing higher levels of IL-8 with lower risk of severe fatigue (Reyes-Gibby et al., 2013). Fatigue symptom in this study was measured by one-item from the 12-Item Short Form Health Survey. On the contrary, IL-8 was not correlated with lung cancer patients' symptom distress including fatigue, and the level of IL-8 was reduced during the 28-day cycle of chemotherapy (Chou et al., 2016). Given that conflicting results about the relationship between IL-8 and fatigue symptom and small number of studies conducted so far, more studies are needed to understand the mechanism of this relationship.

Slope of change in fatigue score was associated with declines in depressive symptom, however, there was no significant association between change of inflammatory cytokines and fatigue symptom over one year. The close associations between depressive symptom and fatigue was similar from previous studies (Di Marco et al., 2006; Doyle et al., 2013; Yohannes & Alexopoulos, 2014). Fatigue symptom was relatively stable compared to depressive symptom over one year in this population. This relationship is also plausible to be bi-directional. Overall, the analyses using CRQ-F as fatigue score showed more significant results compared to SF36-V even though survey questions of both tools are quite similar. It may show that the weakness of subjective measurements to truly measure fatigue symptom.

The hierarchical regression model accounted for 19% of the variance in longitudinal changes of fatigue symptom. It indicates that other factors play a role in COPD-related fatigue symptom. Previous studies suggested symptoms of sleep disturbance and pain, social support,

and self-efficacy may function as predictors of fatigue symptom in COPD (Antoniou & Ungureanu, 2015; Baghai-Ravary et al., 2009).

The clinical meaning of the relationship of inflammatory markers and COPD-related fatigue symptom are still unclear. More studies are needed to understand the underlying mechanisms of the relationship between elevated levels of inflammatory markers measured objectively and fatigue measured subjectively. Systemic inflammation is not constant feature of COPD, and the inflammatory response is a complex networking with various cells and mediators. It is plausible that systematic inflammation is associated with fatigue. However, bidirectional relationships are also possible, especially given the results of insignificant relationship using longitudinal data. Inflammatory cytokines have been known to activate the central nervous system, hypothalamus, pituitary gland, and adrenal glands to cause sickness behavior such as fatigue (Dantzer & Kelley, 2007; MacNee, 2013). They may indirectly cause depression, anxiety, and sleep disorders that can lead to increased fatigue (Dantzer et al., 2014). Fatigue symptom seem to be associated with increased systemic inflammatory markers. It would be clinically applicable in both ways: an effective anti-inflammatory therapy on fatigue as well as an effective fatigue therapy on systemic inflammatory response (Al-shair et al., 2011). The identification of contributing factors of fatigue symptom in COPD will lead to the development of new interventions for fatigue management.

Conclusions

The results of this study indicate an association between CRP and fatigue symptom in COPD. Depressive symptom is also closely associated with fatigue symptom among COPD patients. Longitudinal data over one year described a small change in fatigue is associated with declines in depressive symptoms. More complex models are needed to explain fatigue symptom

in COPD given the modest variance in fatigue symptom. Further studies with longer follow up periods are needed to examine the role of inflammatory biomarkers in the development of fatigue in this population. CRP may serve as a potential biomarker of fatigue symptom in COPD.

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Table 3.1
Sample Characteristics at Baseline (n = 234)

	Mean \pm SD or n(%)
Socio-Demographics	
Age, years	67.4 \pm 8.6
Gender, women	42 (18.0)
Race/Ethnicity	
Caucasians	206 (88.0)
African-American	16 (6.8)
Native Americans/Alaskan Native	6 (2.6)
Asian	3 (1.3)
Other	3 (1.3)
Education	
High school or less	54 (23.1)
Some college or more	180 (76.9)
Income	
< 20K/year	84 (36.0)
\geq 20K/year	149 (64.0)
Marital status	
Partnered	143 (61.1)
Un-partnered	91 (38.9)
Body Mass Index	28.2 \pm 5.9
Current smoker	62 (26.5)
Disease Severity	
FEV1/FVC	0.45 \pm 0.12
FEV1 % predicted	45.6 \pm 15.8
mMRC-Dyspnea	1.9 \pm 1.1
0	18 (7.7)
1	85 (36.3)
2	56 (23.9)
3	58 (24.8)
4	17 (7.3)
Six minute walk distance (feet)	1112.9 \pm 369.7

Note. FEV1 = the forced expiratory volume in one second; FVC = the forced vital capacity; mMRC = the modified Medical Research Council scale (0 = I only get breathless with strenuous exercise; 1 = I get short of breath when hurrying on level ground or walking up a slight hill; 2 = On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace; 3 = I stop for breath after walking about 100 yards or after a few minutes on level ground; 4 = I am too breathless to leave the house or I am breathless when dressing)

Table 3.2
Mean Scores at Baseline and Slope of Change over One Year

Variable Measure	Baseline	Slope of change	Slope Is Different from 0, <i>P</i>
CRQ-F	3.99 ± 1.17	0.41 ± 3.94	.12
SF36-V	46.32 ± 12.61	1.15 ± 11.78	.14
IL-6	1.51 ± 0.71	0.30 ± 0.79	< .001
IL-8	1.62 ± 0.46	0.11 ± 0.49	< .001
CRP	1.52 ± 0.79	0.09 ± 0.87	.13
TNF- α	1.77 ± 0.50	0.16 ± 0.54	< .001
BODE	3.54 ± 2.28	0.14 ± 1.43	.15
HADS-D	4.00 ± 3.97	- 0.89 ± 4.12	< .01
HADS-A	4.90 ± 3.73	- 1.33 ± 3.10	< .001

CRQ-F = Chronic Respiratory Questionnaire - Fatigue subscale ; SF36-V = the Medical Outcomes Study Short Form-36 - Vitality subscale; IL-6 = Interleukin-6; IL-8 = Interleukin-8 ; CRP = C-reactive protein; TNF- α = tumor necrosis factor - alpha ; BODE = **B**ody mass index, **O**bstruction, **D**yspnea, **E**xercise capacity) ; HADS-D = the Hospital Anxiety and Depression Scale - Depression; HADS-A = the Hospital Anxiety and Depression Scale - Anxiety

Table 3.3
Correlations between Fatigue Score and Inflammation Markers at Baseline and After One Year

	CRQ-F	SF36-V	IL-6	IL-8	TNF- α
Baseline					
CRQ-F	1				
SF36-V	.640***	1			
IL-6	-.001	.038	1		
IL-8	.166*	.182**	.542***	1	
TNF- α	.090	.159*	.611***	.623***	1
CRP	-.167*	-.108	.396***	.214**	.154*
Follow-up after one year					
CRQ-F	1				
SF36-V	.681***	1			
IL-6	-.056	-.004	1		
IL-8	.031	.031	.465***	1	
TNF- α	-.046	-.039	.463***	.475***	1
CRP	-.110	-.049	.320***	.074	.0002

* $p < .05$, ** $p < .01$, *** $p < .001$.

CRQ-F = Chronic Respiratory Questionnaire - Fatigue subscale; SF36-V = the Medical Outcomes Study Short Form-36 - Vitality subscale; IL-6 = Interleukin-6; IL-8 = Interleukin-8; TNF- α = tumor necrosis factor - alpha; CRP = C-reactive protein

Table 3.4
Correlations between Slopes of Fatigue Symptom and Inflammation Markers

	CRQ-F	SF36-V	IL-6	IL-8	TNF- α
CRQ-F	1				
SF36-V	.416 ^{***}	1			
IL-6	-.135 [*]	-.024	1		
IL-8	-.113	-.033	.632 ^{***}	1	
TNF- α	-.059	-.050	.609 ^{***}	.686 ^{***}	1
CRP	-.117	-.059	.306 ^{***}	.163 [*]	.062

* $p < .05$, ** $p < .01$, *** $p < .001$.

CRQ-F = Chronic Respiratory Questionnaire - Fatigue subscale; SF36-V = the Medical Outcomes Study Short Form-36 - Vitality subscale; IL-6 = Interleukin-6; IL-8 = Interleukin-8; TNF- α = tumor necrosis factor - alpha; CRP = C-reactive protein

Table 3.5

Multivariate Regression Predicting Fatigue Symptom at Baseline

	Fatigue (CRQ Fatigue)				Fatigue (SF36 Vitality)			
	Beta	SE	95% CI	<i>P</i>	Beta	SE	95% CI	<i>P</i>
Unadjusted								
IL-6	- 0.05	0.15	- 0.38, 0.20	.54	- 0.08	1.59	-4.48, 1.79	.40
IL-8	0.23	0.21	0.17, 1.00	< .01	0.18	2.30	0.39, 9.46	< .05
TNF- α	0.01	0.21	- 0.39, 0.44	.92	0.11	2.28	- 1.66, 7.33	.22
CRP	- 0.20	0.10	- 0.49, -0.09	< .01	- 0.13	1.12	- 4.34, 0.07	.06
Adjusted^a								
IL-6	- 0.04	0.13	- 0.31, 0.19	.64	- 0.06	1.47	-3.96, 1.85	.47
IL-8	0.18	0.19	0.09, 0.84	< .05	0.15	2.16	- 0.30, 8.20	.07
TNF- α	- 0.10	0.19	- 0.61, 0.14	.23	0.01	2.16	- 3.90, 4.63	.87
CRP	- 0.16	0.09	-0.42, -0.06	< .05	- 0.08	1.06	- 3.31, 0.86	.25

^a Adjusted by: age, gender, smoking status, body index, depression, anxiety.

CRQ Fatigue = Chronic Respiratory Questionnaire - Fatigue subscale; SF36 Vitality = the Medical Outcomes Study Short Form-36 - Vitality subscale; IL-6 = Interleukin-6; IL-8 = Interleukin-8; TNF- α = tumor necrosis factor - alpha; CRP = C-reactive protein

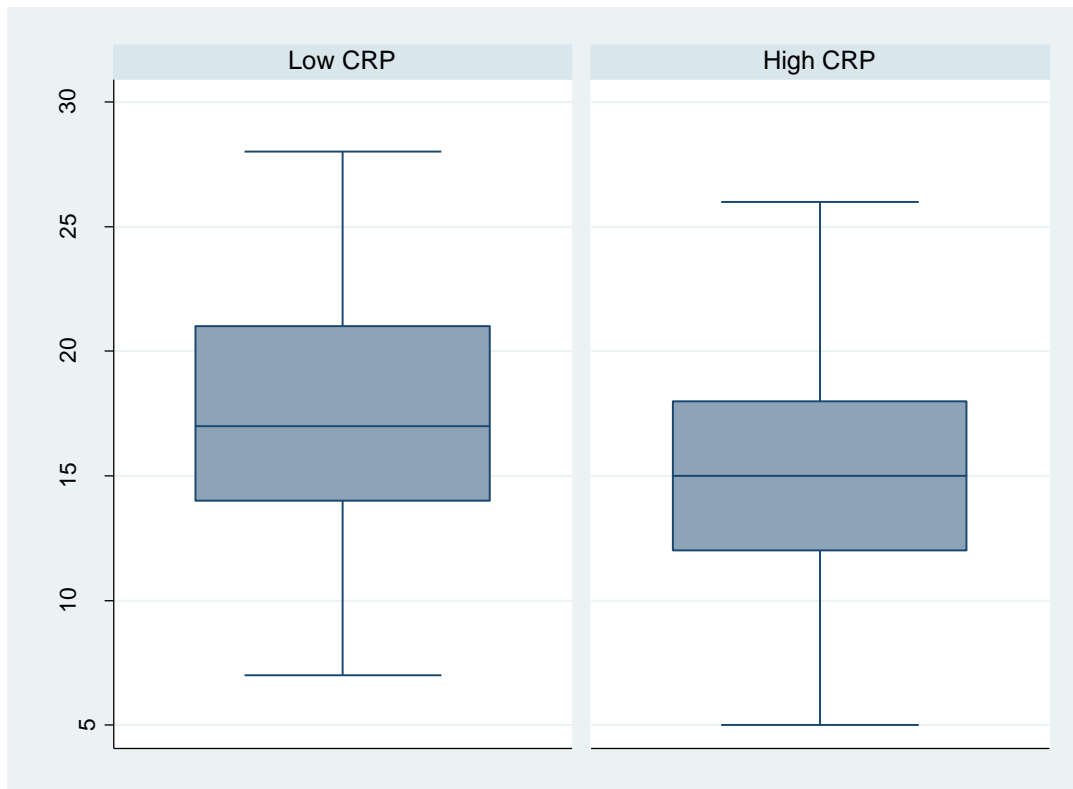
Table 3.6

Hierarchical Regression Predicting Change in Fatigue Symptom over One Year

Independent variables	Cumulative R2	B ± SE	<i>p</i>
Age	.129	0.04 ± 0.007	.57
Gender		- 0.09 ± 0.16	.13
Smoking		0.03 ± 0.14	.68
Baseline fatigue score		- 0.31 ± 0.05	< .001
BODE index	.133	- 0.07 ± 0.04	.26
HADS-A	.184	0.03 ± 0.02	.69
HADS-D		- 0.26 ± 0.02	< .001
IL-6	.191	- 0.04 ± 0.11	.65
IL-8		- 0.09 ± 0.18	.33
TNF- α		- 0.003 ± 0.16	.98
CRP		- 0.06 ± 0.07	.33

BODE = **B**ody mass index, **O**bstruction, **D**yspnea, **E**xercise capacity; HADS-A = the Hospital Anxiety and Depression Scale – Anxiety; HADS-D = the Hospital Anxiety and Depression Scale - Depression; IL-6 = Interleukin-6; IL-8 = Interleukin-8; TNF- α = tumor necrosis factor - alpha; CRP = C-reactive protein

Figure 3.1
Association between CRP Level and CRQ-Fatigue



CRQ Fatigue = Chronic Respiratory Questionnaire - Fatigue subscale; CRP = C-reactive protein

Chapter 4

Conclusions

Patients with chronic obstructive pulmonary disease (COPD) experience moderate to severe fatigue, and awareness of COPD-related fatigue is growing. Fatigue is an important clinical indicator of impaired physical functioning. Other common symptoms occurring for COPD patients include dyspnea and psychological distress. COPD patients often experience multiple symptoms simultaneously and they tend to be interrelated. Adequate symptom management could enhance physical performance for COPD patients, thus potentially improving health outcomes, including quality of life and survival. There are a lack of studies examining the underlying mechanisms of fatigue in COPD and its impact on disease prognosis. The analyses presented in this dissertation are to explore influencing factors and impacts of fatigue for patients with moderate to severe COPD.

In the first paper, we examined the direct effects of dyspnea, anxiety, depressive symptom, and fatigue on physical performance by methods of structural equation modeling. The indirect effects of dyspnea, anxiety, and depressive symptom on physical performance through fatigue was then examined. Results of the analyses found that greater dyspnea was significantly associated with impaired physical performance, while greater anxiety was significantly associated with enhanced physical performance. Fatigue was significantly associated with dyspnea, anxiety, and depressive symptoms. Dyspnea was indirectly associated with fatigue through anxiety and depressive symptoms, and it was the strongest predictor for impaired physical performance. These findings of cross-sectional analyses confirmed that multiple symptoms are usually occurring together and interrelated to each other based on the Theory of Unpleasant Symptoms. Furthermore, common symptoms prevalent in COPD patients have

impacts on their physical functioning. Longitudinal studies are needed to confirm the directionality of these relationships between symptoms and physical performance. It can provide important data for a physical and psychological intervention to improve physical performance for the COPD population.

The aim of the second paper was to explore the association between systemic inflammation and fatigue over one year in patients with moderate to severe COPD. Four inflammatory markers were included C-reactive protein (CRP) and pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor - α . Two inflammatory markers (IL-8 and CRP) were significantly associated with fatigue after adjusting for potential confounders in multivariate analyses when using baseline data. However, in the longitudinal data analyses using slopes of change over one year, there were no significant associations between systemic inflammation and fatigue. The results of this second study indicate systemic inflammation plays a role in the development of fatigue in COPD. Depressive symptoms are also closely associated with fatigue among COPD patients over one year. More complex models are needed to explain fatigue in COPD given the modest variance in the score of fatigue symptom over one year. Further studies with longer follow-up periods are needed to examine the role of inflammatory biomarkers in the development of fatigue in this population. The CRP may serve as a potential biomarker of fatigue in COPD.

The findings of this dissertation research provide information on influencing factors and consequences of fatigue in patients with moderate to severe COPD. Complex relationships among major symptoms in COPD suggest multiple symptoms should be assessed and managed together rather than only focusing on one symptom burden, both in practice and research. In order to better understand underlying mechanisms of fatigue, including systemic inflammation,

more studies that examine multidimensional causes of fatigue are needed in the COPD population.

In practice, nurses are often the first clinicians to listen to patients' complaints about worsening symptom experiences. This is especially important for patients with chronic diseases or several comorbidities since they may have difficult time to differentiate multiple symptoms. Patients with chronic conditions may pay less attention to fatigue and/or other symptoms as they adapt to their diseases. Therefore, the role of nurses to determine occurrences and changes in multiple symptoms as clinical indicators is vital in practice.

In terms of research on the interrelatedness of symptoms, exercise interventions may be beneficial in the reduction of multiple symptom burden, including fatigue in patients with chronic conditions. More research is needed to examine the effects of exercise interventions to relieve symptoms and improve physical functioning. It is essential to examine the long-term effectiveness of exercise interventions on symptom management among patients with chronic diseases since symptom burden may persist for years. Considering the difficulty of differentiating between multiple symptoms among patients with chronic illness, novel phenotypes based on inflammatory markers could be used as indicators of symptom burden. Given that various measurements have been used to assess symptoms across studies showing inconsistent results, it is needed to determine a standardized tool to assess symptoms. Multidimensional measurements for symptom experiences may be useful to accurately assess symptom burden.

VITA

Jun 2016

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EDUCATION

- 2011-2016 **University of Washington** School of Nursing, Seattle, Washington
Ph.D. in Nursing Science (Statistics Area of Concentration)
Doctoral dissertation: Fatigue, physical functioning, and inflammation in patients with chronic obstructive pulmonary disease
Dissertation committee: Monica E. Jarrett, PhD, RN (Chair); Huong Q. Nguyen, PhD, RN; Pamela H. Mitchell, PhD, RN, FAHA, FAAN; Vincent S. Fan, MD, MPH
- 2007-2009 **Yonsei University**, Seoul, Korea, Master of Science in Nursing (MSN)
Master's thesis: Disease knowledge, uncertainty, stress and health behaviors in patients with chronic hepatitis B
- 1999-2004 **Yonsei University**, Seoul, Korea, Bachelors of Science in Nursing (BSN)

PROFESSIONAL EXPERIENCE

- 2014- Graduate Program Evaluation Academic Student Employee, School of Nursing,
present University of Washington
- 2004-2006 Registered Nurse, Division of General Surgery, Severance Hospital, Seoul,
Korea

TEACHING EXPERIENCE

- Mar. 2014- Teaching Assistant, School of Nursing, University of Washington, Seattle, WA
Jun. 2014 Course title: Methods of program evaluation and quality improvement
- Mar. 2011- Part-time Lecturer, College of Nursing, Sungshin University, Seoul, Korea
Jun. 2011 Course title: Fundamentals of Nursing
- Sep. 2010- Part-time Lecturer, College of Nursing, Inha University, Incheon, Korea
Dec. 2010 Course title: Adult nursing practicum
- Jun. 2010- Part-time Lecturer, College of Nursing, Sungshin University, Seoul, Korea
Jul. 2010 Course title: Nursing Informatics
- Sep. 2006- Teaching Assistant, College of Nursing, Yonsei University, Seoul, Korea
Aug. 2009

Course title: Adult nursing practicum (2007-2009), Moderator of the Simulation Lab (2009), Life and death (2009, 2007), Critical care (2009, 2007), Nursing ethics and law (2008), Critical thinking (2008), Pharmacology (2008), Pathophysiology (2007), Chronic diseases management (2007)

RESEARCH EXPERIENCE

- | | |
|------------|--|
| 2011- 2016 | Research Assistant, Depression and functional outcomes in COPD: Impact of genetics and inflammation. PI: Huong Q. Nguyen, National Institutes of Health |
| 2012-2014 | Research Assistant, Contribution of circadian rhythm and maternal entrainment to infant regulation. PI: Karen A. Thomas, National Institutes of Health |
| 2010-2011 | Research Assistant, Longitudinal study about bone health promotion programs for breast cancer survivors. PI: Soo Hyun Kim, The Korean Research Foundation. |
| 2009-2011 | Research Assistant, Strategies to facilitate evidence based nursing in clinical practice. PI: Eui Geum Oh, The Korean Research Foundation. |
| 2009-2010 | Research Assistant, A systematic review of the effectiveness of lifestyle intervention for improving bone health in people at high risk of osteoporosis. PI: Eui Geum Oh, Yonsei University. |
| 2008-2010 | Research Assistant, Interventional research for osteoporosis in at-risk population in community. PI: Eui Geum Oh, Yonsei University. |
| 2008-2009 | Research Assistant, Readiness of evidence based practice among clinical nurses in Korea. PI: Eui Geum Oh, Yonsei University. |
| 2008-2009 | Research Assistant, Attitudes and perceptions on advance directives among people in Korea. PI: Wonhee Lee, Yonsei University. |
| 2008-2009 | Research Assistant, The meaning of prayer in Christian Patients with Breast Cancer. PI: Wonhee Lee, Yonsei University. |
| 2007-2008 | Research Assistant, A study of the effect on leadership and clinical competence of promoting emotional quotient and the control of anger through the coaching program among the registered nurses. PI: Wonhee Lee, The Korean Research Foundation. |
| 2006-2009 | Research Assistant, Therapeutic life style modification for people with metabolic disease in the rural community. PI: Eui Geum Oh, The Korean Science and Engineering Foundation. |
| 2006-2007 | Research Assistant, Development and evaluation of cyber education program for undergraduate students' health promotion. PI: Yoo Ji Soo, Yonsei University. |
| 2006-2007 | Research Assistant, Development of an evidence-based eye care protocol for intensive care unit patients. PI: Yoo Ji Soo, Yonsei University. |

LICENSES, CERTIFICATION

2012-present	Registered Nurse, NY, USA
2004-present	Registered Nurse, Korea

PUBLICATIONS

Peer Reviewed Journal Articles (Published)

1. Fan, V.S., Fleehart, S., Nguyen, H.Q., **Lee, J.**, Kohen, R., Herting, J., Matute-Bello, B., Adams, S.G., Pagalilauan, G., & Borson, S. (December, 2014). Prevalence and correlates of suicidal ideation in patients with COPD: A mixed methods study. *International Journal of Chronic Obstructive Pulmonary Disease*, 9(1), 1321-1329.
2. Thomas, K.A., Burr, R.L., Spieker, S., **Lee, J.**, & Chen, J. (December, 2014). Mother-infant circadian rhythm: Development of individual patterns and dyadic synchrony. *Early Human Development*, 90(12), 885-890.
3. Nguyen, H.Q., Fan, V.S., Herting, J., **Lee, J.**, Fu, M., Chen, Z., Borson, S., Kohen, R., Matute-Bello, B., Pagalilauan, G., & Adams, S.G. (July, 2013). Patients with COPD with higher levels of anxiety are more physically active. *Chest*, 144(1), 145-151.
4. Kim, S.H., Cho, Y.U., Kim, S.J., Lee, J.E., & Kim, J.H. (April, 2013). Low bone density in breast cancer survivors in Korea: prevalence, risk factors and associations with health-related quality of life. *European Journal of Oncology Nursing*, 17(2), 196-203.
5. Oh, E.G., Bang, S.Y., Kim, S.H., Hyun, S.S., Chu, S.H., Jeon, J.Y., Im, J.A., Lee, J.E., & Lee, M.K. (January, 2013). Therapeutic lifestyle modification program reduces plasma levels of the chemokines CRP and MCP-1 in subjects with metabolic syndrome. *Biological Research for Nursing*, 15(1), 48-55.
6. Kim, S.S., Lee, W.H., Cheon, J.Y., **Lee, J.E.**, Yeo, K.S., & Lee, J.H. (2012). Preferences for advance directives in Korea. *Nursing Research and Practice*, 2012, 873892.
7. Oh, E.G., Ko, I.S., Chu, S. H., **Lee, J.E.**, & Yoo, J.Y. (March, 2012). Female college students' knowledge, self-efficacy and health behaviors related to bone health. *Korean Journal of Womens Health Nursing*, 18(1), 38-48.
8. Oh, E.G., Kim, S.H., Bang, S.Y., Hyun, S.S., Im, J.A., Lee, J.E., & Yoo, J.Y. (2012). High-sensitivity C-reactive protein is independently associated with arterial stiffness in women with metabolic syndrome. *Journal of Cardiovascular Nursing*, 27(1), 61-67.

9. Oh, E.G., Bang, S.Y., Kim, S.H., Hyun, S.S., Chu, S.H., Jeon, Y.K., Im, J.A., Lee, M.K., & Lee, J.E. (April, 2011). Effects of a therapeutic lifestyle modification program on inflammatory chemokines and insulin resistance in subjects with metabolic syndrome. *Biological Research for Nursing*, 13(2), 182-188.
10. Kim, J.H., Song, J.E., Lee, S.K., Heo, S.K., Sung, Y.H., & Lee, J.E. (April, 2011). The effect of emotional intelligence on organizational performance in clinical nurses. *The Journal of Korean Academic Society of Nursing Education*, 17(1), 81-90.
11. Lee, J.E., Oh, E.G., Kim, S.S., Kim, S.A., Han, K.H., Kim, S.H., & Jee, E.J. (February, 2011). Disease knowledge, Uncertainty, Stress and Health Behaviors in Patients with Chronic Hepatitis B. *Journal of Korean Academy of Adult Nursing*, 23(1), 20-30.
12. Lee, W.H., Sung, J. H., Lee, J.E., & Kang, K.A. (August, 2010). The Experiences of Prayer in Christian Patients with Breast Cancer. *Journal of Korean Oncology Nursing*, 10(2), 199-209.
13. Oh, E.G., Bang, S.Y., Hyun, S.S., Kim, S.H., Chu, S.H., Jeon, Y.K., Im, J.A., Lee, M.K., & Lee, J.E. (July, 2010). Effect of a 6-Month lifestyle modification intervention on the cardiometabolic risk factors and health-related qualities of life in women with metabolic syndrome. *Metabolism*, 59(7), 1035-1043.
14. Yoo, J.S., Ryue, S.H., Lee, J.E., & Ahn, J.A. (December, 2009). Evaluation of a Complementary Cyber Education Program for a Pathophysiology Class. *Korean Journal of Medical Education*, 21(4), 367-373.
15. Yoo, J.S., Lee, W.H., Kim S.S., Ko, I.S., Oh, E.G., Chu, S.H., Lee, J.H., Kang, S.W., Song, E.K., Chang, S.J., Kim, B.H., & Lee, J.E. (February, 2008). Development of an Eye Care Protocol for ICU patients. *Journal of Korean Academy of Fundamentals of Nursing*, 15(1), 34-44.

Peer Reviewed Journal Articles (In preparation)

1. Lee, J., Jarrett, M., Nguyen, H.Q., Fan, V.S., & Mitchell, P. (in revision). Effects of symptoms on physical performance in COPD patients. *Journal of Pain and Symptom Management*.
2. Lee, J., Jarrett, M., Nguyen, H.Q., Fan, V.S., & Mitchell, P. (in revision). Relationships between inflammation markers and fatigue symptom in COPD patients. *International Journal of Chronic Obstructive Pulmonary Disease*.

Peer Reviewed Conference Abstracts

1. **Lee, J.E.**, Fan, V., Borson, S., Pike, K.C., Jarrett, M.E., & Nguyen, H.Q. (May, 2016). A structural equation modeling analysis of the relationship between symptoms and physical performance in patients with COPD. Oral presented American Thoracic Society Conference, California, USA.
2. **Lee, J.E.**, Yuwen, W., Nguyen, H.Q., & Fan, V. (April, 2015). A Multidimensional model of physical health in patients with COPD. Poster presented at Western Institute of Nursing Conference, New Mexico, USA
3. Nguyen, H.Q., **Lee, J.E.**, Chen, Z., Borson, S., Adams, S.G., Herting, J., & Fan, V. (May, 2014). Associations between cognitive functioning and functional status in COPD. Poster presented at American Thoracic Society Conference, California, USA.
4. **Lee, J.E.**, Cox, P., & Jarrett, M.E. (April, 2014). Clinical outcome of triple therapy in cirrhotic and non-cirrhotic hepatitis C patients. Poster presented at Western Institute of Nursing Conference, Washington, USA.
5. Yip, M.P., Sayre, C., & **Lee, J.E.** (April, 2013). Tai Chi Chuan in Reducing Falls among Community Dwelling Older Adults: A Systematic Review of Randomized Controlled Trials. Poster presented at Western Institute of Nursing Conference, California, USA.
6. **Lee, J.E.**, Fu, M.C., Chen, Z., Albee-Olsen, T., Fan, V., & Nguyen, H.Q. (April, 2012). Factors associated with accelerometry-based physical activity in patients with COPD. Poster presented at Western Institute of Nursing Conference, Oregon, USA.
7. **Lee, J.E.**, Oh, E.G., Kim, S.S., & Kim, S.A. (October, 2009). Disease knowledge, Uncertainty, Stress and Health Behaviors in Patients with Chronic Hepatitis B. Poster presented at The 7th International Nursing Conference, Korean Society of Nursing Science, Seoul, Korea.

AWARDS

2016	Abstract Scholarship Award, American Thoracic Society, USA
2014	Abstract Scholarship Award, American Thoracic Society, USA
2009	Award of Distinction, Graduate School of Yonsei University Thesis Award, Yonsei University, Korea