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Impact of Social Support on Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Impact of Social Support on Patients with Chronic Obstructive Pulmonary Disease

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Background: Chronic obstructive pulmonary disease (COPD) is a common inflammatory disease and is a major cause of morbidity worldwide. Social support has been found to be associated with better self-care behaviors and systemic inflammation in adults as well as in clinical populations. However, little is known about these relationships in patients with COPD. This dissertation is composed of two papers. The purpose of the first paper is to determine the association between social support and self-care behaviors in patients with COPD. The second paper is to examine the association between social support and systemic inflammation in patients with COPD.

Methods: The first paper was a longitudinal study using two-years of follow-up data

from the CASCADE (COPD Activity: Serotonin Transporter, Cytokines, and Depression) cohort (n=282). Self-care behaviors included the following: 1) Physical activity (PA) was measured with a validated accelerometer (Stepwatch) over a 7-day period at baseline, year 1, and year 2; 2) Four yes/no questions on smoking status, participation in pulmonary rehabilitation, and receipt of influenza and/or pneumonia vaccinations; 3) Inhaler/nebulizer medication adherence was based on four questions: carelessness, forgetting, stopping medication when feeling better, and using less of the medication than prescribed when feeling better. Structural social support was measured by self-reported questions on living alone or with others, being partnered, the number of close friends/relatives, and presence of an unpaid caregiver. Functional, or perceived, social support was measured with the Medical Outcomes Social Support Survey (MOSSS). Mixed-effects and logistic regression models were used for the analysis. The second paper was a cross-sectional study using baseline data collected from the CASCADE study. Structural social support was measured by asking whether patients lived alone or with others. Functional social support was measured using the MOSSS total score. Inflammatory biomarkers were measured by tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP). Logistic regression models were used for the analysis.

Results: In 282 participants with moderate to very severe COPD, 80% were men with a mean age of 68 ± 9 . In the first paper, participants who lived with others accrued 903 more steps per day than those who lived alone ($\beta=903$, 95% CI: 373, 1433, $p=0.001$). Higher MOSSS total score ($p=0.03$) and tangible support ($p=0.004$) was

associated with lower odds of smoking. The odds of participation in pulmonary rehabilitation was more than 11 times higher if a patient had a spouse or partner as caregiver compared to not having a caregiver ($p < 0.01$). Perceived social support was associated with marginally higher odds of pneumonia vaccination ($p < 0.05$). There was no significant association between social support and influenza vaccination or adherence with an inhaler or nebulizer medication. In the second paper, in Model 1 (unadjusted), Model 2 (adjusted for age, gender, income, body mass index [BMI], and forced expiratory volume in 1 second percent predicted [FEV1% predicted]), and Model 3 (contains all adjustments from Model 2 with addition of physical activity, current smoking status, depression, and anxiety), neither structural (living with others) nor functional social support were associated with TNF- α , IL-6, or CRP levels. However, physical activity was inversely associated with CRP level ($p < 0.001$).

Conclusions: We found that the type and level of social support had differing effects on core self-care behaviors in patients with COPD. Living with others had a stronger impact on physical activity than functional social support and was associated with a clinically meaningful increase of over +900 steps per day compared to living alone. Having a caregiver was associated with more than a tenfold increase in pulmonary rehabilitation participation compared to having no caregiver. Only functional social support had a small beneficial impact on smoking behavior and pneumococcal vaccinations of unclear clinical significance. Neither structural nor functional support were associated with getting an influenza vaccination or adherence to inhaler or nebulizer medications. Finally, there were no association between social support and

systemic inflammation. Future studies should measure how other social support dimensions, such as ambivalent relationships, impacts self-care behaviors and inflammatory markers in patients with COPD.

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Impact of Social Support on Patients with Chronic Obstructive Pulmonary Disease

INTRODUCTION

Significance of the Problem

Chronic obstructive pulmonary disease (COPD), a common inflammatory disease of the airways and the lung parenchyma, is a major cause of morbidity worldwide. According to the latest World Health Organization (WHO) estimates, 64 million people have COPD and more than 3 million people died from it in 2012.¹ COPD is expected to be the third leading cause of death worldwide by 2030.¹ The goal of caring for patients with COPD includes focusing on symptom palliation and improving quality of life. Research has shown that there is a benefit of social support related health outcomes in patients with COPD.² However, the mechanism underlying this relationship is poorly understood. This dissertation is based on the Broad Model, a conceptual model in which social support impacts biological processes through behavioral and/or psychological pathways.^{3,4}

Social support has been defined as what individuals experience in terms of feeling loved and having a sense of being valued and needed by other people.^{3,4} This also includes factors that promote human development in a social environment.^{5,6} Social support can be conceptualized in terms of two broad domains: structural and functional. Structural social support describes the characteristics of the social network that surrounds a person and his/her interactions within this web of relationships.⁷ It

includes different types of social relations, such as marital status and membership in churches.⁸ Functional social support describes the functions that are provided to a person by a social network, and is commonly classified along five dimensions: emotional, informational, tangible, affectionate, and positive social interaction.⁹

Social support has been reliably related to lower rates of morbidity and mortality. An important issue concerns the physiological mechanisms by which social support influences health outcomes. This could be described by the Broad Model, which was developed by Uchino^{10,11} and has been adapted to COPD and is depicted in Figure 1. The model is based on different theoretical perspectives, including stress-related models of social support and direct effect models of support by Cohen,¹² Berkman, Glass,¹³ Gore,¹⁴ Lin,¹⁵ Thoits,¹⁶ and Umberson.¹⁷ The cyclical links between social support, behavioral, and psychological processes highlight the pathways for understanding how social support influences disease development and health outcomes. Additional behavioral and psychological pathways ultimately influence health outcomes through physiological changes such as systemic inflammation.

Research shows that stronger social support is associated with better self-care behaviors in many chronic diseases.^{18,19} Also, self-care is a key factor in improving health-related quality of life and reducing respiratory-related hospital admissions in patients with COPD.²⁰ However, the evidence for the relationship between social support and self-care behaviors in patients with COPD is unclear.

Many studies have shown that patients with COPD have high levels of systemic inflammatory markers in the blood, such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP).^{21,22} A high CRP level is associated with decreased lung function and low exercise capacity.^{23,24} It has been suggested that chronic inflammation is a key biological mechanism that may affect health outcomes directly (by neural/endocrine/immune biobehavioral pathways) and indirectly (by psychological or behavioral pathways) in patients with COPD. Research across behavioral neuroscience, immunology, and epidemiology has found that both functional and structural social support is associated with systemic inflammation in adults worldwide.²⁵⁻²⁷ In addition, social support predicts inflammation and other symptoms in certain diseases and health problems, such as in breast cancer,²⁸ and depression.²⁹ However, there is no such study conducted of patients with COPD.

Study Purpose

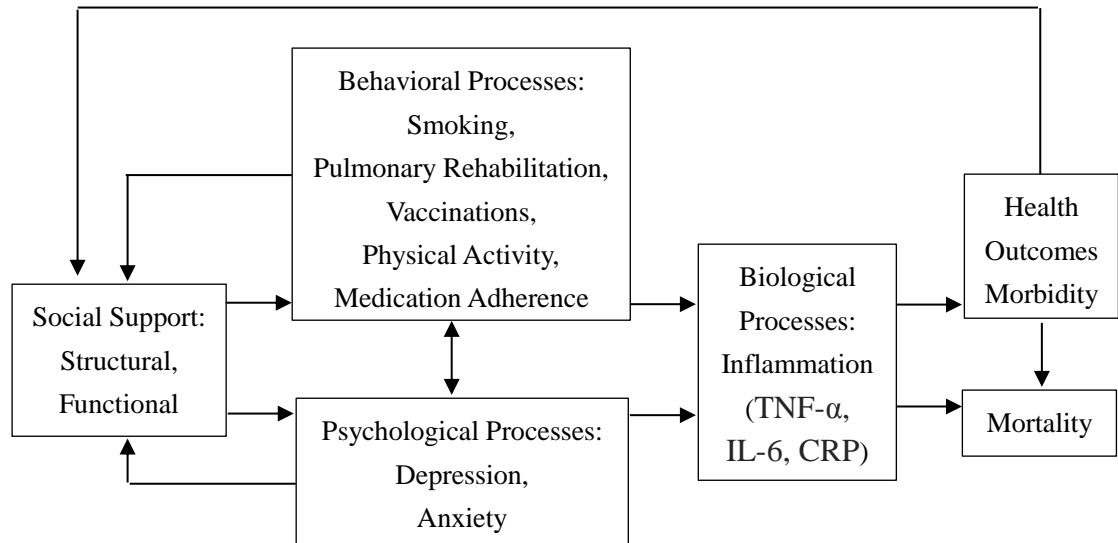
The overall goal of this dissertation was to examine the relationship between social support and the pathways of health outcomes in patients with COPD. The study focused on self-care behaviors and biological processes using the Broad Model (Figure 1). This dissertation used the dataset from the COPD Activity: Serotonin Transporter, Cytokines, and Depression (CASCADE) study.³⁰

Content of the Dissertation

This dissertation consists of two papers. The first paper is to determine the effects of social support on self-care behaviors (physical activity, current smoking

status, participating in pulmonary rehabilitation, receiving vaccinations, and adhering to inhaler or nebulizer medication) in patients with COPD over two years.

The second paper is to examine the association between social support and systemic inflammation (TNF- α , IL-6 and CRP) in patients with COPD.



TNF- α = tumor necrosis factor alpha

IL-6 = interleukin-6

CRP = C-reactive protein

Figure 1: The Broad Model highlights the different levels of analyses by which social support may influence health outcomes in patients with COPD

References

1. World Health Organization. Fact sheet on COPD. <http://www.who.int/mediacentre/factsheets/fs315/en/>. published November 2016. Accessed April 14, 2017
2. Barton C, Effing TW, Cafarella P. Social Support and Social Networks in COPD: A Scoping Review. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2015;12(6):690-702.
3. Cobb S. Presidential Address-1976. Social support as a moderator of life stress. *Psychosomatic medicine*. 1976;38(5):300-314.
4. Kahn RL, Antonucci TC. Convoys over the life course: Attachment, roles, and social support. *Life-span development and behavior*. 1980;3:253-286.
5. Cohen S, McKay G. Social support, stress, and the buffering hypothesis: A theoretical analysis. *Handbook of psychology and health*. 1984;4:253-267.
6. Heaney CA, Israel BA. Social networks and social support. *Health behavior and health education: Theory, research, and practice*. 2002;3:185-209.
7. Heaney CA, Israel BA. Social networks and social support. *Health behavior and health education: Theory, research, and practice*. 2008;4:189-210.
8. Barrera Jr M. Distinctions between social support concepts, measures, and models. *American journal of community psychology*. 1986;14(4):413-445.
9. Sherbourne CD, Stewart AL. The MOS social support survey. *Social science & medicine*. 1991;32(6):705-714.
10. Uchino BN. *Social support and physical health: Understanding the health consequences of relationships*. Yale University Press; 2004.
11. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of behavioral medicine*. 2006;29(4):377-387.
12. Cohen S. Psychosocial models of the role of social support in the etiology of physical disease. *Health psychology*. 1988;7(3):269.
13. Berkman LF, Glass T. Social integration, social networks, social support, and health. *Social epidemiology*. 2000;1:137-173.
14. Gore S. Stress-buffering functions of social supports: An appraisal and clarification of research models. *Stressful life events and their contexts*. 1981:202-222.
15. Lin N. Modeling the effects of social support. *Social support, life events, and depression*. 1986:173-209.
16. Thoits PA. Stress, coping, and social support processes: Where are we? What next? *Journal of health and social behavior*. 1995:53-79.
17. Umberson D. Family status and health behaviors: Social control as a dimension of social integration. *Journal of health and social behavior*. 1987:306-319.
18. Gallant MP. The influence of social support on chronic illness self-management: a review and directions for research. *Health Education &*

-
- Behavior*. 2003;30(2):170-195.
19. Vassilev I, Rogers A, Sanders C, et al. Social networks, social capital and chronic illness self-management: a realist review. *Chronic Illness*. 2011;7(1):60-86.
 20. Zwerink M, Brusse-Keizer M, van der Valk PD, et al. Self management for patients with chronic obstructive pulmonary disease. *The Cochrane Library*. 2014.
 21. Eagan TM, Ueland T, Wagner PD, et al. Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. *European Respiratory Journal*. 2010;35(3):540-548.
 22. Walter RE, Wilk JB, Larson MG, et al. Systemic inflammation and COPD: the Framingham heart study. *Chest Journal*. 2008;133(1):19-25.
 23. Gan WQ, Man S, Senthilselvan A, Sin D. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax*. 2004;59(7):574-580.
 24. De Torres J, Cordoba-Lanus E, Lopez-Aguilar C, et al. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. *European Respiratory Journal*. 2006;27(5):902-907.
 25. Kamiya Y, Whelan B, Timonen V, Kenny RA. The differential impact of subjective and objective aspects of social engagement on cardiovascular risk factors. *BMC geriatrics*. 2010;10(1):81.
 26. Gleib DA, Goldman N, Ryff CD, Lin Y-H, Weinstein M. Social relationships and inflammatory markers: An analysis of Taiwan and the US. *Social Science & Medicine*. 2012;74(12):1891-1899.
 27. Yang YC, Schorpp K, Harris KM. Social support, social strain and inflammation: evidence from a national longitudinal study of U.S. adults. *Social science & medicine (1982)*. 2014;107:124-135.
 28. Hughes S, Jaremka LM, Alfano CM, et al. Social support predicts inflammation, pain, and depressive symptoms: Longitudinal relationships among breast cancer survivors. *Psychoneuroendocrinology*. 2014;42:38-44.
 29. Häfner S, Emeny R, Lacruz M, et al. Association between social isolation and inflammatory markers in depressed and non-depressed individuals: results from the MONICA/KORA study. *Brain, behavior, and immunity*. 2011;25(8):1701-1707.
 30. Nguyen HQ, Fan VS, Herting J, et al. Patients With COPD With Higher Levels of Anxiety Are More Physically Active Depression Anxiety Activity. *CHEST Journal*. 2013;144(1):145-151.

PAPER ONE

Association between Social Support and Self-Care Behaviors in Patients with Chronic Obstructive Pulmonary Disease

Abstract

Rationale: Higher social support is associated with a better quality of life and functioning in patients with chronic obstructive pulmonary disease (COPD).

Objectives: To determine the association between structural and functional social support and six self-care behaviors in patients with COPD.

Methods: This was a longitudinal study using data from participants with physical activity data from the CASCADE (COPD Activity: Serotonin Transporter, Cytokines, and Depression) cohort (n=282).

Measurements and Main Results: Physical activity, a core self-care behavior, was measured with a validated accelerometer (Stepwatch) over a 7-day period at baseline, year 1, and year 2. Additional self-care behaviors included smoking status, participation in pulmonary rehabilitation, and receipt of influenza and/or pneumococcal vaccinations. Inhaler/nebulizer medication adherence was based on four questions: carelessness, forgetting, stopping medication and/or using less of the medication than prescribed when feeling better. Structural social support indicators included living status, being partnered, the number of close friends/relatives, and presence of an unpaid caregiver. Functional social support was measured with the

Medical Outcomes Social Support Survey (MOSSS). Mixed-effects and logistic regression models were used after adjustment for demographic factors, disease severity, medical and psychological comorbidity. Participants who lived with others accrued 903 more steps per day than those who lived alone ($\beta=903$, 95% CI: 373, 1433, $p=0.001$). A one-point increase in the MOSSS total score was associated with 10 more steps per day ($\beta=10$, 95% CI: 2, 18, $p=0.02$). The odds of participation in pulmonary rehabilitation was more than 11 times higher if a patient had a spouse or partner as caregiver compared to not having a caregiver ($p<0.01$). Higher MOSSS total score ($p=0.03$) and tangible support ($p=0.004$) were associated with lower odds of smoking. Functional social support was associated with marginally higher odds of pneumococcal vaccination ($p<0.05$). There was no significant association between social support and influenza vaccination or medication adherence.

Conclusions: Both structural and functional social support were associated with higher physical activity in patients with COPD. Having a caregiver was found to be related to pulmonary rehabilitation attendance. Higher functional social support was related to non-smoking status and higher reception rate of pneumococcal vaccination. Future studies should measure how other aspects of social support impacts self-care behaviors in patients with COPD.

Keywords: social support, self-care, self-management, physical activity, smoking status, pulmonary rehabilitation, vaccination, medication adherence

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease and it is the third leading cause of death in the United States.¹ Management of COPD is typically focused on reducing exacerbation risks and on relieving the impact of symptoms on physical functioning and well-being.² Patients and their families are primarily responsible for undertaking a number of self-care behaviors to successfully manage COPD and other chronic conditions.³⁻⁵ Self-management is a term that is used to describe the process of taking responsibility for one's own day-to-day care to maintain well-being.⁶ For patients with COPD, engaging in regular physical activity, quitting smoking, participating in pulmonary rehabilitation, receiving vaccinations, and adhering to inhaler or nebulizer medication are core behaviors to improve health outcomes.²

Self-management is influenced by a number of factors, including social support.⁷ Social support is the individual's experience of being cared for and loved, and having a sense of being valued and needed by other people, and being part of a mutually supportive network.^{8,9} Social support has been conceptualized as having two domains: structural and functional. Structural social support describes the characteristics of the social network that surrounds a person, and his/her interactions within this network, e.g. marital status and living arrangements.¹⁰ In contrast, functional, or perceived, social support describes the specific functions provided to a person by his/her social network. It can be described using five dimensions—

emotional, informational, tangible, affectionate, and positive social interaction.¹¹

Studies show that higher levels of social support are associated with better self-care behaviors in other chronic diseases such as diabetes, chronic heart disease, and chronic kidney disease.^{7,12} Only a few studies of patients with COPD have reported findings on the effect of social support on self-care behaviors. For example, two studies found that functional social support from family members helped participants manage their COPD.^{13,14} However, none of these studies have systematically examined the influence of both structural and functional support on self-care behaviors in patients with COPD.

Therefore, the purpose of this study is to determine the association between the individual components of structural and functional social support and self-care behaviors (physical activity, smoking status, participating in pulmonary rehabilitation, receiving vaccinations, and adhering to inhaler or nebulizer medication) in patients with COPD. Some of the results from this paper have been previously reported in the form of an abstract.¹⁵

Method

Study Design/Settings

We analyzed data from the COPD Activity: Serotonin Transporter, Cytokines, and Depression (CASCADE) cohort, a multi-site prospective observational study of patients with COPD who were followed for two years to study the biological causes

and functional consequences of depression. We used data collected at three time points (baseline, year 1, and year 2) for this secondary analysis. The CASCADE study was approved by the institutional review boards of the three clinical sites, which included one academic medical center and two Veterans Affairs Health Care Systems in the United States. The study was registered with ClinicalTrials.gov (NCT01074515).

Participants

We recruited participants from queries of medical records and pulmonary function tests, chest clinics from the three medical centers, a research database maintained by the investigators, pulmonary rehabilitation programs, Better Breathers support groups, community pulmonary medicine practices, advertisements, the study web site, and other referrals. The inclusion criteria were: (1) clinical diagnosis of COPD; (2) post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) < 70%; (3) moderate to very severe disease with an FEV_1 < 80% predicted; (4) age \geq 40 years; (5) current or past cigarette smoking ($>$ 10 pack-years); (6) stable disease with no acute exacerbations of COPD in the past 4 weeks; and (7) ability to speak, read, and write English.

Because the CASCADE study was focused on depression and inflammation, we excluded participants with any of the following conditions: other chronic lung diseases (e.g., asthma, bronchiectasis, cystic fibrosis, or idiopathic pulmonary

fibrosis), uncompensated heart failure (with exacerbation in the past 4 weeks), primary pulmonary vascular disease, chronic antibiotic use or ongoing infection, autoimmune disease, lung cancer or metastatic cancer, chronic renal failure requiring dialysis, chronic uncompensated liver disease, HIV/AIDS, or chronic oral prednisone use, bipolar disease, psychotic disorders, and dementia. For this analysis, we further excluded participants from the CASCADE cohort who did not have objective physical activity measurement at baseline (Figure 1-1).

Procedures

All participants provided informed consent before their first clinic assessment which included pre-bronchodilator and post-bronchodilator spirometry and completion of questionnaires. At the end of the clinic visit, participants were asked to wear an activity monitor for 7 days. Two days after this clinic visit, a trained mental-health professional completed a depression and anxiety assessment by telephone. These procedures were repeated one and two years later.

Measures

Demographic data included self-reported age, gender, race, education level, employment status, and household income. Alcohol use was measured with the Audit-C, a 3-item alcohol screen which scored on a scale of 0-12 (scores of 0 reflect no alcohol use). In men, a score of 4 or more is considered positive for

hazardous drinking; in women, a score of 3 or more is considered positive.¹⁶

Spirometry was performed by research coordinators following American Thoracic Society (ATS) standards,¹⁷ and post-bronchodilator values were used in the analyses.

Disease severity measures included the BODE Index¹⁸ and oxygen use.

The BODE Index is a 10-point scale multidimensional grading system that includes weighted scores for body mass index (BMI), airflow obstruction (FEV₁), dyspnea (Modified Medical Research Council Scale), and exercise capacity (6-minute walk test). Comorbidities were measured by self-report using the Charlson Comorbidity Index¹⁹ and participants were categorized as having zero or 1+

comorbidities. *Psychological symptoms* were measured with the Hospital Anxiety and Depression Scale (HADS).²⁰

Social support. Structural social support was measured using three questions: (1) whether participants live alone or live with others; (2) whether they are partnered; and (3) the number of close friends and relatives. Mid-way through the study, we added an additional question regarding the presence of a family/friend caregiver (which family member or friend is most involved in your care now?) and thus have complete data on this variable only at the year 2 assessment. *Functional social support* was measured with the Medical Outcomes Social Support Scale (MOSSS).¹¹ The MOSSS has 20 questions that can be summarized into a total score and four subscales measuring different dimensions of perceived support: emotional/informational, tangible, affectionate, and positive social interaction.

Self-care behaviors. Physical activity (PA) was measured with a Stepwatch 3 Activity Monitor (SAM; OrthoCare Innovations, Washington, D.C.) fastened above the right ankle. The SAM is a highly accurate research grade accelerometer previously validated in patients with COPD.²¹ Participants were asked to wear the SAM during waking hours for 7 days. Total step count per day was the primary physical activity variable.

Other self-care behaviors were based on self-reported responses to four yes/no questions: “In the past week, have you smoked any cigarettes, even a puff? Have you ever participated in an exercise program for your lungs (pulmonary rehabilitation)? In the last year, did you receive an influenza vaccination (flu shot)? Have you received a pneumonia vaccination in the past (pneumovax)?”

Adherence to inhaler or nebulizer medications was measured with four questions about carelessness, forgetting, stopping medication when feeling better, and using less of the medication than prescribed when feeling better in the past 3 months^{22,23} using a 5-point Likert scale from 1 (most of the time) to 5 (none of the time). An adherence score was created by summing responses to these four questions (score range: 4 to 20). Participants were considered fully adherent if they scored a total of 20 points.

Statistical Analysis

Descriptive statistics were used to describe the data over two years of follow up. With the exception of physical activity, none of the other five self-care behaviors

changed significantly at year 1 and 2. Therefore, we used only baseline data to examine the unadjusted and adjusted cross-sectional associations between social support variables (with the exception of caregiver status) and the outcomes of current smoking status, participation in pulmonary rehabilitation, receipt of vaccinations, and adherence with inhaler or nebulizer medication using linear or logistic regression models. One of the structural social support variables, caregiver status, was only ascertained at year 2, and therefore models with caregiver status only used year 2 study data. Each social support variable was included in separate models. Baseline cross-sectional analyses were adjusted for age, gender, race, education level, income, employment status, alcohol use, BODE, home oxygen use, Charlson comorbidity index, HADS-depression, and HADS-anxiety. Due to the smaller sample size for the cross-sectional model of caregiver support and outcomes using the data from year 2, we adjusted for a more limited set of covariates, demographic (age, gender, employment, household income) and disease severity (BODE Index, oxygen use, and Charlson Comorbidity Index).

For physical activity, mixed-effects unadjusted and adjusted models were used to examine relationships between measures of structural/functional social support and physical activity over 2 years. The models contained assessment period (time) as a fixed factor and subject as the random factor. The β coefficient in this model uses the data from all 3 time points to provide an overall estimated effect of social support on PA. Demographics (age, gender, race, education level, income, employment status,

and alcohol use) were fixed (time-invariant) covariates collected only at baseline; disease severity variables (BODE, home oxygen use, and Charlson comorbidity index), and psychological variables (HADS-depression, HADS-anxiety) were assessed at all three time points and were treated as time-varying covariates. With the mixed effects models we were able to include data for all participants who contributed data for at least one follow-up assessment.

All analyses were conducted using Stata 14.0 (StataCorp LP, College Station, Texas). A p value <0.05 was considered statistically significant for all tests without correction for multiple comparisons, as this was an exploratory study.

Results

Sample Characteristics

A total of 302 participants were enrolled in the CASCADE study, however 20 participants were excluded from this analysis due to unusable physical activity data, leaving 282 participants in our baseline study cohort (Figure 1-1). Participant characteristics at baseline, year 1, and year 2 are shown in Table 1-1. The sample included mostly white men (80%) with a mean age of 68 ± 9 . One-third of the participants used supplemental oxygen and half had one or more comorbidities; the mean BODE Index was 4 ± 2 . Self-reported symptoms of depression and anxiety were low.

Overall, participants had relatively high levels of structural and functional social

support. Over half were married or partnered, 75% were living with others, and 90% reported having a family caregiver. The mean total score on the MOSSS was 68 ± 28 .

Participants accrued a mean of 6002 ± 3342 steps per day at baseline with reductions of 474 ± 221 over the two years of follow up. At baseline, 29% were still smoking, 28% had attended a pulmonary rehabilitation program in the past, nearly all had received the influenza or pneumococcal vaccination, and 29% were reported being fully adherent to their inhaler or nebulizer medications.

Social Support and PA

The longitudinal unadjusted and adjusted linear mixed models examining the association between social support and PA over two years are summarized in Table 1-2. We did not find an interaction between functional or structural social support with time when predicting PA. The unadjusted models showed that living with others and having higher levels of perceived social support (total, emotional/informational, and positive social interaction) were significantly associated with higher step counts. In adjusted analyses, participants who lived with others accrued 903 more steps per day than those who lived alone ($\beta=903$, 95% CI: 373, 1433, $p=0.001$). Similarly, perceived social support remained significantly associated with higher step counts in the adjusted models. A one-point increase in MOSSS total score was associated with 10 more steps per day ($\beta=10$, 95% CI: 2, 18, $p=0.02$).

We also examined whether the effect of overall perceived social support

(MOSSS total score) was associated with physical activity after adjusting for structural support (living situation) in the same model over two years. The unadjusted analysis showed that both living with others and having higher levels of total functional social support were significantly and independently associated with higher step counts. However, after adjusting for covariates, only living with others remained associated with higher step counts over the two year period ($\beta=812$, 95% CI: 264, 1359, $p=0.004$). The cross-sectional year 2 analysis showed that the presence of a family caregiver did not have an effect on step counts.

Social Support and Pulmonary Rehabilitation

Logistic regression analyses showed that living with others, being married or partnered, and having 6 or more close friends or relatives were not associated with previous participation in pulmonary rehabilitation (Table 1-3). However, the odds of participation in pulmonary rehabilitation was more than five times higher if a patient had a caregiver compared to no caregiver ($p<0.05$). After adjusting for covariates, the odds of participation in pulmonary rehabilitation was 11 times higher when patients had a spouse or partner as their caregiver compared to those without a caregiver ($p<0.01$). Functional social support was not associated with attending pulmonary rehabilitation.

Social Support and Current Smoking Status

The adjusted logistic regression analyses showed that none of the structural social support measures were associated with current smoking status (Table 1-4). While functional social support had a statistically significant relationship with smoking status, the effects were modest.

Social Support and Vaccinations

While there was no relationship between structural or perceived social support and influenza vaccination, perceived social support was associated with marginally higher odds of pneumococcal vaccination in adjusted models (Table 1-5).

Social Support and Adherence with Inhaler or Nebulizer Medication

There was no significant association between structural or perceived social support and adherence with inhaler or nebulizer medication.

Discussion

We found that the type and level of social support had differing effects on core self-care behaviors in patients with COPD. Living with others had a stronger impact on physical activity than functional social support and was associated with a clinically meaningful increase of over +900 steps per day compared to living alone.²⁴ Having a caregiver was associated with more than a tenfold increase in pulmonary rehabilitation participation compared to having no caregiver. Only functional social

support had a small beneficial impact on smoking behavior and pneumococcal vaccinations of unclear clinical significance. Neither structural nor functional support were associated with getting an influenza vaccination or adherence to inhaler or nebulizer medications.

Since higher levels of physical activity have been shown to be associated with lower risk of exacerbations, hospitalizations and all-cause mortality in COPD,²⁵⁻²⁸ our finding that living with others and having a higher perception of overall social support positively influence physical activity is especially important. To our knowledge, this is the first longitudinal study on the relationship between structural and functional social support and PA in patients with COPD.

It is important to note that patients who reported living with others rated far higher levels of functional social support across all four MOSSS subscales (+15 to 27 points) compared to those who lived alone. The presence of a caregiver had no influence on physical activity. Thus, it is reasonable to surmise that the physical proximity of living with others matters more in terms of opportunities for positive social interactions that results in greater engagement in both self-care and social activities in and outside the home. In an earlier study, Donesky et al. found that living with others was associated with a higher frequency, duration, and continuity of walking in patients with COPD²⁹ but that study did not measure functional social support. More recently, Mesquita et al reported on a cross-sectional study of cohabitating patient-family member dyads in the Netherlands and found that patients

with COPD who lived with more active family members had higher levels of physical activity than those with living with an inactive family member.³⁰ Furthermore, loneliness has been shown to be associated with lower levels of physical activity in healthy older adults.³¹

We did not find an interaction between functional or structural social support with time when predicting PA, suggesting that the rate of change in PA did not vary by level of social support over 2 years of follow-up. At all 3 time points, higher social support was associated with increased PA, however, higher social support does not protect patients from declines in PA over time. Although PA is expected to decline with disease progression,³² living with others may be one of many important factors that contribute to patients' daily physical activities through greater opportunities for reciprocal social interactions. It is therefore important to consider how to incorporate social support and interactions into interventions that aim to increase PA. More detailed study of these processes are warranted since optimizing living arrangements is potentially modifiable in some situations.

Pulmonary rehabilitation is integral in the management of COPD.² However, participation in, and adherence to, pulmonary rehabilitation remains very poor.^{33,34} There was a high rate of participation in pulmonary rehabilitation in our sample, which is not an accurate reflection of uptake in the general U.S. COPD population and is more a function of where we targeted our recruitment efforts for the main study. We found that while living with others and being partnered were not associated with

participation in a pulmonary rehabilitation program prior to enrollment in our study, having a spouse or partner as a *caregiver* had a strong influence on participation. This is not surprising since our question specifically asked if patients had a family or friend who is most involved in their care. Our finding is consistent with previous studies reporting that lack of encouragement and support from family and friends were associated with non-participation and non-adherence to pulmonary rehabilitation.³⁵⁻³⁷ We recognize there are a number of other barriers to participation in pulmonary rehabilitation beyond social support, e.g. transportation challenges, access, insurance coverage, motivation, that we were unable to account for in our analysis.

Smoking is the main cause of COPD,² and is associated with an increased risk of COPD exacerbations.³⁸ Accordingly, identifying factors associated with smoking cessation is a high priority. In this study, we found that both structural and functional social support had little if any notable relationship with smoking behavior. Previous studies have found that smoking cessation in patients with COPD is more related to worse disease severity, use of smoking cessation medications, and having health insurance.³⁹ It is unclear how best to incorporate social or family support to help patients with COPD quit smoking⁴⁰ though there are some evidence to suggest that people with high levels of partner support and perceived social support are more successful at quitting smoking.⁴¹⁻⁴³

Influenza and pneumococcal vaccination are important primary and secondary prevention strategies to prevent exacerbations in patients with COPD.^{2,44-46} The lack

of variation in influenza vaccination in our study may partly explain why we did not find any relationship between social support and influenza vaccination as 85% of the sample reported receiving an influenza vaccination. Interestingly, Burns et al found that community-dwelling older adults who lived with others were more likely to report influenza vaccination than those living alone.⁴⁷ We found that higher functional social support was associated with modest higher odds of pneumococcal vaccination.

Pharmacological treatment helps to reduce symptoms and exacerbations in COPD.² We found that neither structural nor functional social support was associated with adherence to inhaler or nebulizer medication. Using the same adherence measure, Khmour et al also found that neither marital status nor living arrangements were associated with medication adherence in COPD.⁴⁸ However, in another large study that relied on both subjective (self-reporting) and objective (canister weight change) measurement of adherence over a 2-year period, participants who were married were more likely to adhere to their inhalers compared to unmarried individuals.⁴⁹ In a cross-sectional study using pharmacy refill data, Trivedi et al, found that caregivers, especially spouses, improved medication adherence in patients with COPD compared to patients without caregivers.⁵⁰ These inconsistent findings may be due to the different adherence measurements used across studies, and the fact that we used a self-report measure of adherence.

Limitations

Several limitations are worth noting. The majority of our sample were men, most of whom had attended some college, many with a history of military service who were relatively active and had low levels of depression and anxiety and thus our findings may not generalize to larger COPD population. While we measured both structural and functional social support, we did not measure other potentially important dimensions of social relationships such as family conflict and cohesion that might have adverse influences on self-care behaviors.⁵¹ In addition, since most of the dependent variables did not change over time with the exception of PA, we were only able to examine cross-sectional relationships between social support and self-care behaviors. Finally, the lack of correction for multiple comparisons may have resulted in spurious associations in these exploratory analyses but we were careful to not over interpret our findings.

Conclusion

Our finding that structural social support as measured by reports of living with others and having a caregiver were respectively, associated with higher levels of physical activity and greater participation in pulmonary rehabilitation in patients with COPD reinforces the critical importance of the social environment in shaping patients' success with self-care. While our findings should be replicated in larger, more representative samples, we believe that efforts to engage patients in these core self-care behaviors must at the very least, routinely assess for and tangibly assist

patients in marshalling the necessary social support to maximize their chances of effecting positive change.

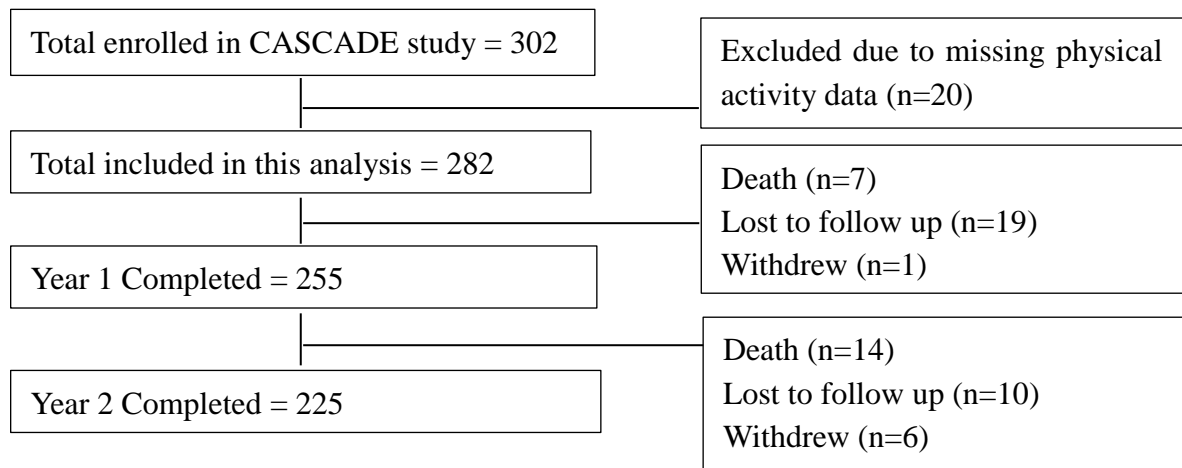


Figure 1-1. Study Sample Flowchart

Table 1-1. Sample Characteristics

Variables	Baseline (n=282)	Y1 (n=255)	Y2 (n=225)
Age, years	67.7 ± 8.6	68.6 ± 8.6	69.6 ± 8.6
Gender, Male	226 (80%)	203 (80%)	181 (80%)
Race, Caucasian/White	246 (87%)	225 (88%)	201 (89%)
Education, Some college or more	218 (77%)	197 (77%)	176 (78%)
Income, ≥20K/year	172 (62%)	161 (64%)	141 (64%)
Currently employed	42 (15%)	39 (15%)	25 (11%)
Alcohol misuse*	54 (19%)	44 (17%)	39 (17%)
FEV1% predicted	44.9 ± 15.7	46.5 ± 16.7	44.9 ± 17.3
BODE Index (↓0-10)	3.7 ± 2.3	3.5 ± 2.3	3.4 ± 2.4
O2 supplementation	98 (34%)	91 (36%)	93 (41%)
Charlson comorbidity index ≥1	138 (49%)	121 (48%)	109 (48%)
HADS-Depression (↓0-21)	4.2 ± 4.1	3.2 ± 4.0	3.0 ± 3.3
HADS-Anxiety (↓0-21)	5.0 ± 3.9	3.6 ± 3.8	3.3 ± 3.6
Structural social support			
Marital status: Partnered	163 (58%)	147 (58%)	124 (55%)
Live with others	211 (75%)	190 (75%)	162 (72%)
Report having 6+ close friends or relatives	125 (44%)	112 (45%)	108 (48%)
Presence of unpaid caregiver [†]			n=215
Partner	N/A	N/A	117 (54%)
Other (child, sibling, friend)	N/A	N/A	76 (35%)
None	N/A	N/A	22 (10%)

Variables	Baseline (n=282)	Y1 (n=255)	Y2 (n=225)
Functional social support			
MOSSS, Total (0-100↑)	68.4 ± 27.8	73.8 ± 24.9	73.5 ± 25.1
Emotional/informational	66.7 ± 28.3	71.8 ± 25.1	72.8 ± 25.8
Tangible	70.5 ± 29.4	73.6 ± 26.9	73.2 ± 29.1
Affectionate	72.0 ± 32.3	78.6 ± 28.9	76.7 ± 30.1
Positive social interaction	70.6 ± 30.2	76.1 ± 27.0	75.4 ± 27.0
Self-care behaviors			
Physical activity, total steps/day	6001.5 ± 3341.8	5830.6 ± 3260.7	5527.7 ± 3121.0
Current smoker	86 (29%)	67 (25%)	60 (25%)
Participation in pulmonary rehabilitation	83 (28%)	84 (32%)	82 (35%)
Received influenza vaccination in the last year	262 (87%)	234 (88%)	201 (85%)
Received pneumococcal vaccination in the past	252 (84%)	223 (84%)	200 (85%)
Full adherence with inhaler or nebulizer medication	81 (29%)	77 (31%)	70 (32%)

Data are presented as n (%) or mean ± SD. Direction of arrows represent scores reflecting better health. HADS = Hospital Anxiety and Depression Scale, MOSSS = Medical Outcomes Social Support Survey

* Possible alcohol misuse based on an Audit C score ≥4 in men or ≥3 in women

↑ indicates that higher scores are better health

↓ indicates that lower scores are better health

† Since this question was added after the study started, we only have data for the second year of follow up.

Table 1-2. Associations between Social Support and Physical Activity

Models [†]	Unadjusted			Adjusted*		
	B	<i>p</i>	95%CI	B	<i>p</i>	95%CI
Structural social support						
Live with others	779.7	< 0.01	227.2, 1372.3	903.0	< 0.01	372.8, 1433.2
Married/partnered	454.8	0.12	-113.1, 1022.8	490.1	0.07	-31.5, 1011.8
6+ friends and relatives	-117.5	0.50	-459.6, 224.6	-149.4	0.40	-497.1, 198.4
Caregiver [‡]						
No caregiver	Ref	Ref	Ref	Ref	Ref	Ref
Spouse or partner	-388.9	0.61	-1881.8, 1103.9	453.3	0.48	-803.8, 1710.4
Other	-1061.7	0.18	-2617.7, 494.2	-3.3	0.99	-1281.0, 1274.4
Functional social support: MOSSS scores						
Total	11.8	< 0.01	3.5, 20.2	10.1	0.02	1.9, 18.3
Emotional and informational	10.9	< 0.01	3.0, 18.8	9.1	0.02	1.3, 16.8
Tangible	6.0	0.12	-1.5, 13.5	5.9	0.11	-1.3, 13.2
Affectionate	5.0	0.16	-1.9, 11.9	3.8	0.27	-2.9, 10.5
Positive social interaction	9.0	0.01	1.9, 16.1	7.9	0.03	0.8, 14.9

MOSSS=Medical Outcomes Study Social Support Scale

* Adjusted for year, age, gender, race, education level, income, employment status, alcohol use, BODE, home oxygen use, Charlson comorbidity index, HADS-depression, and HADS-anxiety.

† Each social support measure was modeled separately.

‡ Only year 2 data used for caregiver analyses. Reference group of caregiver was patients without caregiver. Model adjusted for age, gender, income, employment status, BODE, home oxygen use, and Charlson comorbidity index.

Table 1-3. Associations between Social Support and Pulmonary Rehabilitation

Models [†]	Unadjusted			Adjusted*		
	OR	p	95%CI	OR	p	95%CI
Structural social support						
Live with others	0.92	0.79	0.51, 1.67	1.29	0.49	0.64, 2.60
Married/partnered	1.14	0.64	0.67, 1.92	1.43	0.28	0.75, 2.72
6+ close friends and relatives	1.38	0.23	0.82, 2.32	1.53	0.16	0.84, 2.77
Caregiver[‡]						
No caregiver	Ref	Ref	Ref	Ref	Ref	Ref
Spouse or partner	5.75	0.02	1.28, 25.84	11.03	<0.01	1.93, 62.97
Other	5.51	0.03	1.20, 25.39	4.34	0.10	0.77, 24.31
Functional social support: MOSSS scores						
Total	1.00	0.49	0.99, 1.01	1.00	0.52	0.99, 1.01
Emotional and informational	1.01	0.34	1.00, 1.01	1.01	0.27	1.00, 1.02
Tangible	1.00	0.81	0.99, 1.01	1.00	0.97	0.99, 1.01
Affectionate	1.01	0.23	1.00, 1.01	1.00	0.32	1.00, 1.01
Positive social interaction	1.00	0.47	1.00, 1.01	1.00	0.38	0.99, 1.01

MOSSS=Medical Outcomes Study Social Support Scale

*Adjusted for age, gender, race, education level, income, employment status, alcohol use, BODE, home oxygen use, Charlson comorbidity index, HADS-depression, and HADS-anxiety

† Each social support measure was modeled separately.

‡ Only year 2 data used for caregiver analyses. Reference group of caregiver was patients without caregiver. Model adjusted for age, gender, income, employment status, BODE, home oxygen use, and Charlson comorbidity index

Table 1-4. Associations between Social Support and Current Smoking Status

Models [†]	Unadjusted			Adjusted*		
	OR	p	95%CI	OR	p	95%CI
Structural social support						
Live with others	1.01	0.97	0.55, 1.86	0.79	0.51	0.39, 1.60
Married/partnered	0.87	0.60	0.51, 1.48	0.91	0.76	0.48, 1.71
6+ close friends and relatives	0.71	0.21	0.41, 1.21	0.92	0.79	0.49, 1.72
Caregiver[‡]						
No caregiver	Ref	Ref	Ref	Ref	Ref	Ref
Spouse or partner	0.32	0.02	0.12, 0.82	0.52	0.25	0.17, 1.59
Other	0.19	<0.01	0.07, 0.53	0.37	0.10	0.11, 1.20
Functional social support: MOSSS scores						
Total	0.99	<0.01	0.98, 1.00	0.99	0.03	0.98, 1.00
Emotional and informational	0.99	0.03	0.98, 1.00	0.99	0.11	0.98, 1.00
Tangible	0.99	<0.01	0.98, 0.99	0.98	<0.01	0.97, 1.00
Affectionate	0.99	0.04	0.98, 1.00	0.99	0.14	0.98, 1.00
Positive social interaction	0.99	0.03	0.98, 1.00	0.99	0.06	0.98, 1.00

MOSSS=Medical Outcomes Study Social Support Scale

*Adjusted for age, gender, race, education level, income, employment status, alcohol use, BODE, home oxygen use, Charlson comorbidity index, HADS-depression, and HADS-anxiety

† Each social support measure was modeled separately.

‡ Only year 2 data used for caregiver analyses. Reference group of caregiver was patients without caregiver. Model adjusted for age, gender, income, employment status, BODE, home oxygen use, and Charlson comorbidity index

Table 1-5. Associations between Social Support and Pneumococcal Vaccination

Models [†]	Unadjusted			Adjusted*		
	OR	p	95%CI	OR	p	95%CI
Structural social support						
Live with others	1.17	0.67	0.57, 2.43	1.23	0.62	0.53, 2.85
Married/partnered	1.39	0.32	0.72, 2.66	0.98	0.96	0.46, 2.11
6+ close friends and relatives	1.60	0.17	0.82, 3.16	1.26	0.57	0.57, 2.77
Caregiver [‡]						
No caregiver	Ref	Ref	Ref	Ref	Ref	Ref
Spouse or partner	0.91	0.89	0.24, 3.40	0.60	0.49	0.14, 2.54
Other	0.89	0.87	0.23, 3.49	0.83	0.80	0.19, 3.59
Functional social support: MOSSS scores						
Total	1.02	<0.01	1.01, 1.03	1.02	0.02	1.00, 1.03
Emotional and informational	1.02	<0.01	1.01, 1.03	1.02	<0.01	1.01, 1.03
Tangible	1.02	<0.01	1.01, 1.03	1.02	0.02	1.00, 1.03
Affectionate	1.01	<0.01	1.01, 1.02	1.01	0.04	1.00, 1.02
Positive social interaction	1.01	0.02	1.00, 1.02	1.01	0.07	1.00, 1.02

MOSSS=Medical Outcomes Study Social Support Scale

*Adjusted for age, gender, race, education level, income, employment status, alcohol use, BODE, home oxygen use, Charlson comorbidity index, HADS-depression, and HADS-anxiety

[†] Each social support measure was modeled separately.

[‡] Only year 2 data used for caregiver analyses. Reference group of caregiver was patients without caregiver. Model adjusted for age, gender, income, employment status, BODE, home oxygen use, and Charlson comorbidity index

References

1. National Heart, Lung, and Blood Institute. What Is COPD? <http://www.nhlbi.nih.gov/health/health-topics/topics/copd>. Published July 2013. Accessed April 14, 2017
2. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 Report. *Respirology*. 2017;22(3):575-601.
3. Jordan RE, Majothi S, Heneghan NR, et al. Supported self-management for patients with moderate to severe chronic obstructive pulmonary disease (COPD): an evidence synthesis and economic analysis. *Health Technology Assessment*. 2015;19(36):1.
4. Nici L, Bontly TD, ZuWallack R, Gross N. Self-management in chronic obstructive pulmonary disease. Time for a paradigm shift? *Annals of the American Thoracic Society*. 2014;11(1):101-107.
5. Deek H, Hamilton S, Brown N, et al. Family - centred approaches to healthcare interventions in chronic diseases in adults: a quantitative systematic review. *Journal of advanced nursing*. 2016;72(5):968-979.
6. Lorig KR, Holman HR. Self-management education: history, definition, outcomes, and mechanisms. *Annals of behavioral medicine*. 2003;26(1):1-7.
7. Gallant MP. The influence of social support on chronic illness self-management: a review and directions for research. *Health Education & Behavior*. 2003;30(2):170-195.
8. Cassel J. The contribution of the social environment to host resistance. *American journal of epidemiology*. 1976;104(2):107-123.
9. Cobb S. Presidential Address-1976. Social support as a moderator of life stress. *Psychosomatic medicine*. 1976;38(5):300-314.
10. Barrera Jr M. Distinctions between social support concepts, measures, and models. *American journal of community psychology*. 1986;14(4):413-445.
11. Sherbourne CD, Stewart AL. The MOS social support survey. *Social science & medicine*. 1991;32(6):705-714.
12. Vassilev I, Rogers A, Sanders C, et al. Social networks, social capital and chronic illness self-management: a realist review. *Chronic Illness*. 2011;7(1):60-86.
13. Xiaolian J, Chaiwan S, Panuthai S, Yijuan C, Lei Y, Jiping L. Family support and self - care behavior of Chinese chronic obstructive pulmonary disease patients. *Nursing & health sciences*. 2002;4(1 - 2):41-49.
14. Kara Kasikci M, Alberto J. Family support, perceived self-efficacy and self-care behaviour of Turkish patients with chronic obstructive pulmonary disease. *Journal of clinical nursing*. 2007;16(8):1468-1478.
15. Chen Z, Fan VS, Pike KC, et al. The Impact Of Social Support On Changes In Physical Activity Over 2-Years In Patients With COPD. In: Proceedings of the 2016 American Thoracic Society International Conference; May 13-18, 2016; San Francisco, CA, US. Abstract A4524

-
16. Bush K, Kivlahan DR, McDonnell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Archives of internal medicine*. 1998;158(16):1789-1795.
 17. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *European respiratory journal*. 2005;26(2):319-338.
 18. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *New England Journal of Medicine*. 2004;350(10):1005-1012.
 19. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. *Journal of clinical epidemiology*. 1996;49(12):1429-1433.
 20. Ng T-P, Niti M, Tan W-C, Cao Z, Ong K-C, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Archives of Internal Medicine*. 2007;167(1):60-67.
 21. Nguyen HQ, Burr RL, Gill DP, Coleman K. Validation of the StepWatch device for measurement of free-living ambulatory activity in patients with chronic obstructive pulmonary disease. *Journal of nursing measurement*. 2011;19(2):76-90.
 22. Brooks CM, Richards JM, Kohler CL, et al. Assessing adherence to asthma medication and inhaler regimens: a psychometric analysis of adult self-report scales. *Medical care*. 1994:298-307.
 23. Morisky DE, Ang A, Krousel - Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *The Journal of Clinical Hypertension*. 2008;10(5):348-354.
 24. Demeyer H, Burtin C, Hornikx M, et al. The minimal important difference in physical activity in patients with COPD. *PloS one*. 2016;11(4):e0154587.
 25. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Ant ó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax*. 2006;61(9):772-778.
 26. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPDPhysical activity and all-cause mortality in COPDA prospective Cohort Study. *CHEST Journal*. 2011;140(2):331-342.
 27. Moy ML, Gould MK, Liu I-LA, Lee JS, Nguyen HQ. Physical activity assessed in routine care predicts mortality after a COPD hospitalisation. *ERJ Open Research*. 2016;2(1):00062-02015.
 28. Nguyen HQ, Chu L, Amy Liu I-L, et al. Associations between physical activity and 30-day readmission risk in chronic obstructive pulmonary disease. *Annals of the American Thoracic Society*. 2014;11(5):695-705.
 29. Donesky D, Janson SL, Nguyen HQ, Neuhaus J, Neilands TB, Carrieri-Kohlman V. Determinants of frequency, duration, and continuity of home walking in patients with COPD. *Geriatric nursing (New York, NY)*.

-
- 2011;32(3):178-187.
30. Mesquita R, Nakken N, Janssen DJ, et al. Activity levels and exercise motivation in COPD patients and their resident loved ones. *Chest*. 2017;151(5):1028-1038.
 31. Hawkey LC, Thisted RA, Cacioppo JT. Loneliness predicts reduced physical activity: cross-sectional & longitudinal analyses. *Health Psychology*. 2009;28(3):354.
 32. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. *European Respiratory Journal*. 2009;33(2):262-272.
 33. Keating A, Lee A, Holland AE. What prevents people with chronic obstructive pulmonary disease from attending pulmonary rehabilitation? A systematic review. *Chronic respiratory disease*. 2011;8(2):89-99.
 34. Garrod R, Marshall J, Barley E, Jones PW. Predictors of success and failure in pulmonary rehabilitation. *The European respiratory journal*. 2006;27(4):788-794.
 35. Hayton C, Clark A, Olive S, et al. Barriers to pulmonary rehabilitation: characteristics that predict patient attendance and adherence. *Respiratory medicine*. 2013;107(3):401-407.
 36. Young P, Dewse M, Fergusson W, Kolbe J. Respiratory rehabilitation in chronic obstructive pulmonary disease: predictors of nonadherence. *European Respiratory Journal*. 1999;13(4):855-859.
 37. Arnold E, Bruton A, Ellis-Hill C. Adherence to pulmonary rehabilitation: a qualitative study. *Respiratory medicine*. 2006;100(10):1716-1723.
 38. Au DH, Bryson CL, Chien JW, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. *Journal of general internal medicine*. 2009;24(4):457-463.
 39. Hilberink SR, Jacobs JE, Schlosser M, Grol RP, de Vries H. Characteristics of patients with COPD in three motivational stages related to smoking cessation. *Patient Educ Couns*. 2006;61(3):449-457.
 40. Luker KA, Chalmers KI, Caress AL, Salmon MP. Smoking cessation interventions in chronic obstructive pulmonary disease and the role of the family: a systematic literature review. *Journal of advanced nursing*. 2007;59(6):559-568.
 41. Mermelstein R, Cohen S, Lichtenstein E, Baer JS, Kamarck T. Social support and smoking cessation and maintenance. *Journal of consulting and clinical psychology*. 1986;54(4):447.
 42. Murray RP, Johnston JJ, Dolce JJ, Lee WW, O'Hara P. Social support for smoking cessation and abstinence: The Lung Health Study. *Addictive behaviors*. 1995;20(2):159-170.
 43. Westmaas JL, Bontemps-Jones J, Bauer JE. Social support in smoking cessation: reconciling theory and evidence. *Nicotine & Tobacco Research*. 2010;12(7):695-707.
 44. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the

-
- effectiveness of influenza vaccination: a randomized controlled study. *CHEST Journal*. 2004;125(6):2011-2020.
45. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax*. 2006;61(3):189-195.
 46. Lee TA, Weaver FM, Weiss KB. Impact of pneumococcal vaccination on pneumonia rates in patients with COPD and asthma. *Journal of general internal medicine*. 2007;22(1):62-67.
 47. Burns VE, Ring C, Carroll D. Factors influencing influenza vaccination uptake in an elderly, community-based sample. *Vaccine*. 2005;23(27):3604-3608.
 48. Khmour MR, Hawwa AF, Kidney JC, Smyth BM, McElnay JC. Potential risk factors for medication non-adherence in patients with chronic obstructive pulmonary disease (COPD). *European journal of clinical pharmacology*. 2012;68(10):1365-1373.
 49. Rand CS, Nides M, Cowles MK, Wise RA, Connett J. Long-term metered-dose inhaler adherence in a clinical trial. The Lung Health Study Research Group. *American journal of respiratory and critical care medicine*. 1995;152(2):580-588.
 50. Trivedi RB, Bryson CL, Udris E, Au DH. The influence of informal caregivers on adherence in COPD patients. *Annals of Behavioral Medicine*. 2012;44(1):66-72.
 51. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. *Health psychology*. 2004;23(2):207.

PAPER TWO

Social Support and Inflammatory Markers in Patients with Chronic Obstructive Pulmonary Disease

Abstract

Objective: Social support is associated with systemic inflammation in older adults as well as in clinical populations. However, these relationships have not been studied in patients with chronic obstructive pulmonary disease (COPD). The purpose of this study was to examine the association between social support and systemic inflammation in patients with COPD.

Methods: This was a cross-sectional study using baseline data collected from a multi-site prospective observational study of COPD from September 2011 to March 2015 in the United States. Structural social support was measured by asking whether patients lived alone or with others. Functional social support was measured using the Medical Outcomes Study (MOS) Social Support Survey total score. Inflammatory biomarkers were measured by tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP). Logistic regression models predicted those with TNF- α , IL-6, and CRP levels > 75th percentile using social support and other covariates.

Results: In 302 moderate to very severe COPD participants, 80% were men with a mean age of 68 \pm 9. In Model 1 (unadjusted), Model 2 (adjusted for age, gender, income, BMI, FEV1% predicted), and Model 3 (contains all adjustments from Model

2 with addition of physical activity, current smoking status, depression, and anxiety), neither structural (living with others) nor functional social support were associated with TNF- α , IL-6, or CRP levels.

Conclusions: These findings suggest that the biologic processes are still unclear in the relationship between social support and inflammatory markers in patients with COPD. Using larger and more diverse sample sizes, and more sensitive measures of social support should be considered in future studies.

Keywords: COPD, social support, live with others, physical activity, depression, inflammatory markers

Introduction

Chronic obstructive pulmonary disease (COPD), a common inflammatory disease of the airways and the lung parenchyma, is a major cause of morbidity worldwide. Research has shown that social support is associated with improved health outcomes in patients with COPD.¹ Social support is what individuals experience in terms of feeling loved and having a sense of being valued and needed by other people.^{2,3} Social support can be conceptualized in terms of two broad domains: structural and functional. Structural social support, also known as social integration, describes the characteristics of the social network that surrounds a person, and his/her interactions within this web of relationships.⁴ Functional social support describes the functions that are provided to a person by a social network, and is commonly classified along five dimensions: emotional, informational, tangible, affectionate, and positive social interaction.⁵

Drawing from many animal and human studies, Cassel posited that social support is a key psychosocial “protective” factor that is likely to play a nonspecific role in the etiology of diseases.⁶ Since then, many studies have attempted to understand the mechanism of how social support influences the incidence and prevalence of a wide array of health outcomes. Inflammation, a protective response that involves immune cells, and molecular mediators, drove the attention of many recent empirical research studies. Many studies showed that inflammatory markers, e.g. C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) are prognostic factors for many chronic conditions, such as cardiovascular

disease, type 2 diabetes, arthritis, and Alzheimer's disease.^{7,8} CRP is produced predominantly by hepatocytes in response to a wide variety of stimuli.⁹ IL-6 is the most important known inducer of CRP production; TNF- α can induce CRP production as well.¹⁰

COPD is characterized by both airway and systemic inflammation, which increase as the disease progresses.¹¹ Systemic inflammation in patients with COPD is associated with weight loss, cardiovascular diseases, and osteoporosis.¹² Stable COPD patients have higher levels of TNF- α , IL-6, and CRP than non-COPD patients.¹³ Moreover, CRP level also have been reported as a strong and independent predictor of hospitalization and mortality in COPD.^{14,15} It has been suggested that chronic inflammation is a key biological mechanism that may affect health outcomes directly (by neural/endocrine/immune biobehavioral pathways) and indirectly (by psychology or behavior pathways) in patients with COPD.

Research across behavioral neuroscience, immunology, and epidemiology has found that both functional and structural social support is associated with systemic inflammation in community-dwelling adults and older adults.¹⁶⁻¹⁸ In clinical populations, higher level of social support was associated with lower levels of inflammation and symptoms in breast cancer survivors,¹⁹ and individuals with depression.²⁰ However, these relationships have not been studied in patients with COPD. The purpose of this study is to examine the association between functional and structural social support and systemic inflammation in patients with stable COPD.

Methods

Study Design/Settings

This was a cross-sectional study using baseline data collected from 302 patients from the *COPD Activity: SERT, Cytokines, and Depression (CASCADE)* cohort. The CASCADE study is a multi-site prospective observational study of COPD participants who were followed for two years to study the biological causes and functional consequences of depression. The CASCADE study was approved by the respective institutional review boards at three clinical sites: one academic medical center and two Veterans Affairs Health Care Systems (VAHCS). The study was registered with ClinicalTrials.gov (NCT01074515).

Participants

We recruited participants from queries of medical records and pulmonary function tests, chest clinics from the three medical centers, a research database maintained by the investigators, pulmonary rehabilitation programs, Better Breathers groups, community pulmonary medicine practices, advertisements, the study web site, and other referrals. The inclusion criteria were: 1) clinical diagnosis of COPD; 2) post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) < 70%; 3) moderate to very severe disease with an FEV_1 < 80%; 4) Age \geq 40 years; 5) current or past cigarette smoking (> 10 pack-years); 6) stable disease as defined as no acute exacerbations of COPD in the past 4 weeks; and 7) ability to speak, read, and write English.

Patients with any of the following conditions were excluded from the study: other chronic obstructive lung diseases (such as asthma, bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis), uncompensated congestive heart failure (with exacerbation in the past 4 weeks), primary pulmonary vascular disease, and non-COPD-related chronic inflammatory diseases, infectious diseases or auto-immune diseases, 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 dementia.

Procedures

Informed consent was obtained prior to the baseline clinical assessments, which included pre- and post-bronchodilator spirometry and completion of questionnaires. A total of 10 ml of whole blood was obtained from the antecubital vein after a 20 minute resting period to measure biomarkers of inflammation.

Measures

Structural social support was measured by asking whether patients lived alone or with others. *Functional social support* was measured using the Medical Outcomes Study (MOS) Social Support Survey total score. The MOS has a total of 19 items with a Cronbach's alpha of 0.97 and has been used widely.^{5,21-23}

Inflammatory markers included hs-CRP, IL-6, and TNF- α . Peripheral blood was

collected between 9:30 AM and 4:00 PM into vacutainer tubes with ethylenediaminetetraacetic acid anticoagulant at each in-clinic assessment. Plasma was obtained by centrifugation at 2000 X g for 10 minutes. Samples were stored in a -70 °C refrigerator. The TNF- α and IL-6 were measured using the Luminex multiplex platform with Millipore Milliplex High Sensitivity Human Cytokine Magnetic Beads. The lower limit of detection was 0.13 pg/mL. The concentration of hs-CRP was measured by duoset enzyme-linked immunosorbent assay (ELISA) (R&D Systems) with 15.5 pg/mL lower limit of detection. Values greater than the 75th percentile was considered “high” for TNF- α (>6.81 pg/mL) and IL-6 (>5.03 pg/mL). For CRP, levels >3.0 mg/L was considered “high”.²⁴

Demographic data included age, gender, and self-reported household income. Spirometry was performed by research coordinators according to the American Thoracic Society (ATS) standards²⁵ using a handheld spirometer. Post-bronchodilator values were used. *Disease severity* measures included the body mass index (BMI) (kg/m²), and forced expiratory volume in 1 second percent predicted (FEV1% predicted). *Health behaviors* included physical activity and current smoking status. Physical activity was measured with a Stepwatch[®] 3 Activity Monitor (SAM; OrthoCare Innovations, Washington D.C.) fastened above the right ankle. The SAM has been validated for use in patients with COPD.²⁶ Participants were asked to wear the SAM during waking hours for seven days. Total step count per day was used to compute the physical activity variable. Current smoking status was measured through self-report: “In the past week, have you smoked any cigarettes, even a puff?”

Psychological well-being was measured with the Hospital Anxiety and Depression Scale (HADS).²⁷

Statistical Analysis

This was a cross-sectional analysis. COPD patients' social support, inflammatory markers, demographic, clinical, health behaviors, and psychological well-being characteristics were analyzed using descriptive statistics. Inflammatory markers were reported as being in the median and interquartile range (IQR). Continuous variables were reported as means \pm standard deviation (SD), and categorical variables as frequencies (%). In Model 1, we used logistic regression to explore the relationship between measures of structural and functional social support and inflammation. TNF- α , IL-6, and CRP were treated as dichotomous variables (TNF- α and IL-6: >75th percentile vs low; CRP: >3 mg/L vs low). In Model 2 we used a multivariate logistic regression model, which adjusted for potential confounders of the relationship between social support and inflammation including age, gender, income, BMI, and FEV1% predicted. Model 3 included additional adjustments for health behaviors (physical activity and smoking status) and psychological well-being (depression and anxiety). We adjusted for variables that were significantly associated with social support and/or inflammatory markers in our models. All analyses were conducted using Stata 14.0 (StataCorp LP, College Station, Texas). A *p* value <0.05 was considered statistically significant.

Results

Table 1 presents the characteristics of the 302 participants. Data on inflammatory markers and physical activity were missing for 2 and 20 participants, respectively.

The sample included mostly men (80%) with a mean age of 68 ± 9 . Sixty-two percent had an annual income greater than \$20K and 28% were current smokers. The mean BMI was 28 ± 6 , FEV1% predicted was 45 ± 16 , and total steps/day of 6002 ± 3342 . Symptoms of depression and anxiety were low.

Overall, participants had relatively high levels of structural and functional social support. 74% lived with others and the mean total score on the MOS Social Support Survey was 68 ± 28 . The median level and IQR of TNF- α , IL-6, and CRP were 5 [3 – 7] pg/mL, 3 [2 – 5] pg/mL, and 3 [2 – 6] mg/L, respectively. A quarter of the sample had “high” levels of TNF- α (>6.81 pg/mL) and IL-6 (>5.03 pg/mL) exceeding the 75th percentile and 53% had high levels of CRP (>3.0 mg/ml).

Tables 2-4 shows the results of the individual step-wise logistic regression models for TNF- α , IL-6, and CRP, respectively. Across all models and adjustments, neither structural (living with others) nor functional social support were associated with TNF- α , IL-6, or CRP levels.

Other covariates, however, were associated with these inflammatory markers in COPD. For TNF- α , in model 2, age was associated with higher TNF- α levels ($p = 0.013$). An increase of one year was associated with about increasing 5% odds of being above the 75th percentile of TNF- α level. Increased BMI was associated with higher IL-6 and CRP levels ($p < 0.001$). An increase of one point of BMI score was

associated with an increase of about 9% of having high levels of IL-6 level and 8% CRP level.

Model 3 assesses the roles of health behavioral and psychological well-being factors as potential mediators or confounders of the relationship between social support and inflammatory markers. Although our data did not show any relationship between most of these variables and levels of inflammatory markers, physical activity was inversely associated with CRP level ($p < 0.001$).

Discussion

A number of epidemiological studies have explored both direct and indirect associations between dimensions of social support and level of inflammation in healthy and clinical populations.¹⁶⁻²⁰ To our best knowledge, this is the first study to explore this relationship in patients with COPD. We did not find any association between structural and functional social support with three key inflammatory markers (TNF- α , IL-6, or CRP). In contrast to previous large scale epidemiological studies of heterogeneous populations with sample sizes ranging from 805 to 14,818 participants,^{16,17,20,28-34} our negative findings reflect a lack of affect of social support on inflammation in COPD, or may be due to the smaller sample size, homogenous group of stable COPD patients who had relatively low levels of inflammation, or use of different and possibly less sensitive measures of social support.

Structural Social Support and Inflammation

The association between higher structural social support and lower inflammation

have been relatively consistent across previous studies with samples that ranged from 805 to 14,818 participants. Seven studies that used the Social Network Index (SNI)³⁵ or similar SNI measures found that structural social support scores were negatively related to CRP level among healthy adults and older adults, patients with coronary heart disease or cancer.^{16,28-33} Two studies found that SNI scores were negatively associated with IL-6 in adults,^{20,33} but one did not find any relationship.³² One study that combined CRP, plasma fibrinogen, and serum albumin into an inflammation-burden index showed that lower SNI was associated with higher inflammation burden in cancer patients.³¹ The negative findings from our study may be because we used a simple structural measure of support (living with others) versus the SNI which includes a composite measure of marital status, frequency of interactions with friends and family, religious attendance, and membership in social organizations

Functional Social Support and Inflammation

The relationship between functional social support and inflammation is mixed. Three studies reported that higher levels of functional social support was associated with lower levels of inflammation (CRP, IL-6, and TNF- α).^{34,36,37} Low support measured by the emotional social support (ESS) index was associated with high levels of CRP and IL-6 in healthy adults but after adjustments, the relationship only remained for CRP in men but not in women.³⁴ Another study found that low perceived social support was associated with increased TNF- α levels in healthy adults.³⁶

Breast-cancer survivors with lower pretreatment social support had higher IL-6 levels over 6 months.³⁷ However, two studies using the English Longitudinal Study of Ageing (ELSA) cohort found no significant relationship between functional social support and inflammation.^{17,29} Neither perception of loneliness²⁹ nor emotional social support¹⁷ were related with CRP levels. Another study of healthy middle age adults actually found that higher perceived social support was associated with higher CRP and soluble IL-6 receptor (sIL-6R) levels.¹⁶

Demographic and COPD Severity Variables

Our study adjusted for age, gender, income, BMI and FEV1% predicted in model 2. Many studies showed that age and gender had a significant relationship with CRP and IL-6 levels. In the Ford et al study, with 14,818 participants, social networks were inversely associated with CRP level in men aged greater than 60 years, but not in younger men or women.³⁰ Additionally, three epidemiology studies that focused on older adults, whose average age was above 70 years, found similar results.^{29,32,38} Social networks and low emotional social support were found to be inversely associated with IL-6³³ and CRP^{30,32,34} in men, but not in women. In our study, we found that age had a significant relationship with TNF- α but there was no difference between genders. It could be because 80% of the participants were men.

Income was not only associated with social support,³⁹ but was also associated with a greater burden of inflammation. In many national population-based studies, income was significantly negatively associated with TNF- α , IL-6, and CRP.⁴⁰⁻⁴² BMI

and FEV1% predicted are very important parameters to assess functional status of patients with COPD.⁴³ Thus we also included these variables in our analysis.

Health Behaviors

Social support influences health behaviors, such as physical activity and smoking. It has been demonstrated in several prospective studies that social support was significantly associated with physical activity,^{44,45} and predicts successful smoking cessation.^{46,47} In addition, physical activity and smoking have been demonstrated to be significantly associated with inflammation, such CRP and IL-6 levels.⁴⁸⁻⁵⁰

In our study, we adjusted for physical activity and current smoking status as health behaviors in Model 3. Previous studies found that after adjusting for health behaviors, both structural and functional social support have a relationship with inflammatory markers, such as CRP and IL-6.^{16,17,30,33,34} In addition, two of these studies found that adjusting for these health behaviors decreased the odds ratio between social network/social engagement and CRP.^{17,30} Similarly, in the association between emotional social support and inflammation, one study found that after adjustment for health behavior factors, only CRP, not IL-6, remained significantly associated with low emotional social support.³⁴ These results suggest that these health behavior factors are responsible for mediating or confounding the association between social support and inflammation. Although in our study, we did not find an association between social support and inflammatory markers, we did examine the relationship between health behaviors and inflammation. To our knowledge, our study is the first

study to use objective measurement to measure physical activity, instead of self-reporting in a model of the effect of social support on inflammation. We found that total daily steps account was inversely associated with CRP level. Future study should explore the relationship between physical activity and inflammatory markers using objective measurement.

Psychological Well-Being

The other major pathway involves psychological processes that are linked to emotions or moods in the relationship between social support and inflammatory markers. There are many studies showing important associations between social support and depression/anxiety.^{51,52} Depression and anxiety also has been associated with elevated IL-6 and CRP levels.⁵³⁻⁵⁶

In previous studies, there was evidence for psychological pathways linking social support to inflammation. One study found that depressed and socially isolated significantly increased IL-6 and CRP levels, in comparison with non-depressed and socially integrated men.²⁰ Similarly, another study found that after adjustment for depression, social network was significantly associated with IL-6 in men, but not in women.³³ However, in a longitudinal study, depressive symptoms did not predict emotional social support or IL-6 over time. IL-6 also did not relate to change in emotional social support.¹⁷ This study found that the emotional social support/IL-6/depressive symptoms change process is unidirectional, rather than reciprocal. However, there is no study focusing on other psychological characteristics.

In our study, we add anxiety as a psychological well-being factor, since it is also highly related to social support and biological processes.^{57,58}

Limitations

Although we measured both structural and functional social support in our study, we did not measure the potential negative aspects higher structural or functional social support. People living with others may have ambivalent relationships which may have negative effects on well-being. One study found that positive social support from family, friends, and spouse protected against risks of inflammation, while negative social support (social strain) from family and friends increased inflammation risk.¹⁸ And negative social relationships were stronger than positive associations of social support with inflammation.¹⁸ Future studies should address more the quality of social support, and will provide additional insight into the role of inflammatory markers as biological mediators between social support and health outcomes.

Conclusion

This cross-sectional study examined the association between social support and inflammatory markers in patients with COPD. We found no relationship between living with others or perceived social support and TNF- α , IL-6, or CRP. This study also identified possible behaviors and physiologic pathways that are associated with social support and inflammatory markers. These findings suggest that the biologic mechanism evidence of the connection between social support and inflammatory

markers in patients with COPD is still unclear. Future studies could explore this relationship by using larger and more diverse sample sizes, and different measures.

Table 2-1. Sample characteristics

Variables	Baseline
Demographic variables	
Age, years	67.6 ± 8.6
Gender, Men	243 (80%)
Race, Caucasian/White	246 (87%)
Education, Some college or more	218 (77%)
Income, >20K/year	184 (62%)
COPD severity variables	
BMI	28.1 ± 6.1
FEV1% predicted	45.0 ± 15.8
Oxygen supplementation	98 (34%)
Charlson comorbidity index ≥1	138 (49%)
Health Behaviors	
Physical Activity: Total step counts/day	6001.5 ± 3341.8
Current smoker	86 (28%)
Psychological Well-Being	
HADS-Depression (↓0-21)	4.2 ± 4.1
HADS-Anxiety (↓0-21)	5.0 ± 3.9
Social support	
Live with others	223 (74%)
MOSSS, Total Score (0-100↑)	67.9 ± 27.7
Inflammatory markers	
TNF-α: Median [IQR]	4.7 [3.3 – 6.8]
IL-6: Median [IQR]	2.9 [1.8 – 5.0]
CRP: Median [IQR]	3.3 [1.5 – 6.0]
TNF-α (>75 th percentile)	75 (25%)
IL-6 (>75 th percentile)	75 (25%)
CRP (>3.0 mg/L)	159 (53%)

Data are presented as n (%) or mean ± SD. Direction of arrows represent scores reflecting better health. BMI = Body Mass Index, FEV1 = Forced Expiratory Volume 1, HADS = Hospital Anxiety and Depression Scale, MOSSS = Medical Outcomes Social Support Survey, TNF-α = Tumor necrosis factor-alpha, IL-6 = Interleukin-6, CRP = C-reactive protein

↑ indicates that higher scores are better health

↓ indicates that lower scores are better health

Table 2-2. Logistic regression models to predict TNF- α

	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Live with others	1.50 (0.75, 3.01)	1.51 (0.71, 3.22)	1.40 (0.64, 3.05)
MOSSS total score	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)
Age		1.05 (1.01, 1.08)*	1.05 (1.01, 1.09)*
Gender		0.57 (0.24, 1.34)	0.53 (0.22, 1.29)
Income		0.91 (0.50, 1.68)	0.82 (0.44, 1.54)
BMI		1.04 (0.99, 1.08)	1.04 (0.99, 1.10)
FEV1% predicted		1.01 (1.00, 1.03)	1.01 (0.99, 1.03)
Physical activity			1.00 (0.99, 1.01)
Smoking status			1.02 (0.49, 2.12)
Depression			0.93 (0.85, 1.03)
Anxiety			1.05 (0.95, 1.17)

MOSSS = Medical Outcomes Social Support Survey, BMI = Body Mass Index, FEV1 = Forced Expiratory Volume 1, TNF- α = Tumor necrosis factor-alpha

*P<0.05

Model 1 unadjusted

Model 2 controls for age, gender, income, BMI, FEV1% predicted

Model 3 contains all adjustments from Model 2 with addition of health behaviors and psychological well-being

Table 2-3. Logistic regression models to predict IL-6

	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Live with others	0.85 (0.44, 1.63)	0.84 (0.40, 1.75)	0.98 (0.46, 2.10)
MOSSS	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Age		1.03 (1.00, 1.07)	1.01 (0.97, 1.06)
Gender		0.69 (0.31, 1.55)	0.79 (0.34, 1.83)
Income		1.44 (0.77, 2.70)	1.47 (0.77, 2.82)
BMI		1.09 (1.04, 1.14)***	1.07 (1.02, 1.13)**
FEV1% predicted		1.02 (1.00, 1.04)	1.02 (1.00, 1.04)*
Physical activity			0.99 (0.98, 1.00)
Smoking status			0.77 (0.36, 1.65)
Depression			0.95 (0.85, 1.04)
Anxiety			0.99 (0.89, 1.10)

MOSSS = Medical Outcomes Social Support Survey, BMI = Body Mass Index, FEV1 = Forced Expiratory Volume 1, IL-6 = Interleukin-6

*P<0.05; **p<0.01; ***p<0.001

Model 1 unadjusted

Model 2 controls for age, gender, income, BMI, FEV1% predicted

Model 3 contains all adjustments from Model 2 with addition of health behaviors and psychological well-being

Table 2-4. Logistic regression models to predict CRP

	Unadjusted	Model 1	Model 2
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Live with others	1.43 (0.80, 2.55)	1.32 (0.70, 2.48)	1.80 (0.90, 3.60)
MOSSS	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Age		0.98 (0.95, 1.01)	0.97 (0.93, 1.00)
Gender		0.75 (0.39, 1.44)	0.96 (0.47, 1.96)
Income		1.06 (0.63, 1.78)	1.37 (0.78, 2.40)
BMI		1.08 (1.04, 1.13)***	1.08 (1.03, 1.14)**
FEV1% predicted		1.00 (0.98, 1.01)	1.01 (0.99, 1.03)
Physical activity			0.98 (0.97, 0.99)***
Smoking status			1.86 (0.98, 3.61)
Depression			1.02 (0.94, 1.11)
Anxiety			0.96 (0.88, 1.05)

MOSSS = Medical Outcomes Social Support Survey, BMI = Body Mass Index, FEV1 = Forced Expiratory Volume 1, CRP = C-reactive protein

p<0.01; *p<0.001

Model 1 unadjusted

Model 2 controls for age, gender, income, BMI, FEV1% predicted

Model 3 contains all adjustments from Model 2 with addition of health behaviors and psychological well-being

Reference

1. Barton C, Effing TW, Cafarella P. Social Support and Social Networks in COPD: A Scoping Review. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2015;1-13.
2. Cobb S. Presidential Address-1976. Social support as a moderator of life stress. *Psychosomatic medicine*. 1976;38(5):300-314.
3. Kahn RL, Antonucci TC. Convoys over the life course: Attachment, roles, and social support. *Life-span development and behavior*. 1980;3:253-286.
4. Heaney CA, Israel BA. Social networks and social support. *Health behavior and health education: Theory, research, and practice*. 2008;4:189-210.
5. Sherbourne CD, Stewart AL. The MOS social support survey. *Social science & medicine*. 1991;32(6):705-714.
6. Cassel J. The contribution of the social environment to host resistance. *American journal of epidemiology*. 1976;104(2):107-123.
7. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annual review of medicine*. 2000;51(1):245-270.
8. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annual review of psychology*. 2002;53(1):83-107.
9. Hirschfield G, Pepys M. C-reactive protein and cardiovascular disease: new insights from an old molecule. *Qjm*. 2003;96(11):793-807.
10. Wolz J. Contemporary Clinical Immunology and Serology Rittenhouse-Olson, De Nardin Pearson, 2013. *Immunological investigations*. 2013;42(3):262-262.
11. Agust íA. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proceedings of the American Thoracic Society*. 2007;4(7):522-525.
12. Bailey KL, Goraya J, Rennard SL. The Role of Systemic Inflammation in COPD. *Chronic Obstructive Pulmonary Disease*: Springer; 2012:15-30.
13. Gan WQ, Man S, Senthilselvan A, Sin D. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax*. 2004;59(7):574-580.
14. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine*. 2007;175(3):250-255.
15. Man S, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax*. 2006;61(10):849-853.
16. Gleib DA, Goldman N, Ryff CD, Lin Y-H, Weinstein M. Social relationships and inflammatory markers: An analysis of Taiwan and the US. *Social Science & Medicine*. 2012;74(12):1891-1899.
17. Kamiya Y, Whelan B, Timonen V, Kenny RA. The differential impact of

-
- subjective and objective aspects of social engagement on cardiovascular risk factors. *BMC geriatrics*. 2010;10(1):81.
18. Yang YC, Schorpp K, Harris KM. Social support, social strain and inflammation: Evidence from a national longitudinal study of US adults. *Social Science & Medicine*. 2014;107:124-135.
 19. Hughes S, Jaremka LM, Alfano CM, et al. Social support predicts inflammation, pain, and depressive symptoms: longitudinal relationships among breast cancer survivors. *Psychoneuroendocrinology*. 2014;42:38-44.
 20. Häfner S, Emeny R, Lacruz M, et al. Association between social isolation and inflammatory markers in depressed and non-depressed individuals: results from the MONICA/KORA study. *Brain, behavior, and immunity*. 2011;25(8):1701-1707.
 21. Dafaalla M, Farah A, Bashir S, et al. Validity and reliability of Arabic MOS social support survey. *SpringerPlus*. 2016;5(1):1306.
 22. Yu DS, Lee DT, Woo J. Psychometric testing of the Chinese version of the medical outcomes study social support survey (MOS - SSS - C). *Research in nursing & health*. 2004;27(2):135-143.
 23. Anderson D, Bilodeau B, Deshaies G, Gilbert M, Jobin J. [French-Canadian validation of the MOS Social Support Survey]. *The Canadian journal of cardiology*. 2005;21(10):867-873.
 24. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. *Circulation*. 2003;107(3):499-511.
 25. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *European respiratory journal*. 2005;26(2):319-338.
 26. Nguyen HQ, Burr RL, Gill DP, Coleman K. Validation of the StepWatch device for measurement of free-living ambulatory activity in patients with chronic obstructive pulmonary disease. *Journal of nursing measurement*. 2011;19(2):76-90.
 27. Ng T-P, Niti M, Tan W-C, Cao Z, Ong K-C, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. *Archives of Internal Medicine*. 2007;167(1):60-67.
 28. Heffner KL, Waring ME, Roberts MB, Eaton CB, Gramling R. Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. *Social Science & Medicine*. 2011;72(9):1482-1488.
 29. Shankar A, McMunn A, Banks J, Steptoe A. Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology*. 2011;30(4):377.
 30. Ford ES, Loucks EB, Berkman LF. Social integration and concentrations of C-reactive protein among US adults. *Annals of epidemiology*.

-
- 2006;16(2):78-84.
31. Yang YC, Li T, Frenk SM. Social Network Ties and Inflammation in US Adults with Cancer. *Biodemography and social biology*. 2014;60(1):21-37.
 32. Loucks EB, Berkman LF, Gruenewald TL, Seeman TE. Relation of social integration to inflammatory marker concentrations in men and women 70 to 79 years. *The American journal of cardiology*. 2006;97(7):1010-1016.
 33. Loucks EB, Sullivan LM, D'AGOSTINO Sr RB, Larson MG, Berkman LF, Benjamin EJ. Social networks and inflammatory markers in the Framingham Heart Study. *Journal of biosocial science*. 2006;38(06):835-842.
 34. Mezuk B, Diez Roux AV, Seeman T. Evaluating the buffering vs. direct effects hypotheses of emotional social support on inflammatory markers: the multi-ethnic study of atherosclerosis. *Brain, behavior, and immunity*. 2010;24(8):1294-1300.
 35. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American journal of Epidemiology*. 1979;109(2):186-204.
 36. Copertaro A, Bracci M, Manzella N, Barbaresi M, Copertaro B, Santarelli L. Low Perceived Social Support Is Associated with CD8+CD57+ Lymphocyte Expansion and Increased TNF- α Levels. *BioMed research international*. 2014;2014:1-5
 37. Hughes S, Jaremka LM, Alfano CM, et al. Social support predicts inflammation, pain, and depressive symptoms: Longitudinal relationships among breast cancer survivors. *Psychoneuroendocrinology*. 2014;42:38-44.
 38. Sbarra DA. Marriage protects men from clinically meaningful elevations in C-reactive protein: results from the National Social Life, Health, and Aging Project (NSHAP). *Psychosomatic medicine*. 2009;71(8):828-835.
 39. Brummett BH, Barefoot JC, Vitaliano PP, Siegler IC. Associations among social support, income, and symptoms of depression in an educated sample: the UNC Alumni Heart Study. *International journal of behavioral medicine*. 2003;10(3):239-250.
 40. Friedman EM, Herd P. Income, education, and inflammation: differential associations in a national probability sample (the MIDUS study). *Psychosomatic Medicine*. 2010;72(3):290.
 41. Koster A, Bosma H, Penninx BW, et al. Association of inflammatory markers with socioeconomic status. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2006;61(3):284-290.
 42. Alley DE, Seeman TE, Kim JK, Karlamangla A, Hu P, Crimmins EM. Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. *Brain, behavior, and immunity*. 2006;20(5):498-504.
 43. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 Report. *Respirology*. 2017;22(3):575-601.
 44. Donesky D, Janson SL, Nguyen HQ, Neuhaus J, Neilands TB, Carrieri-Kohlman V. Determinants of frequency, duration, and continuity of

-
- home walking in patients with COPD. *Geriatric nursing (New York, NY)*. 2011;32(3):178-187.
45. McAuley E, Blissmer B, Marquez DX, Jerome GJ, Kramer AF, Katula J. Social relations, physical activity, and well-being in older adults. *Preventive medicine*. 2000;31(5):608-617.
 46. Lindström M, Isacson SO, Group MSNS. Smoking cessation among daily smokers, aged 45–69 years: a longitudinal study in Malmö, Sweden. *Addiction*. 2002;97(2):205-215.
 47. Roski J, Schmid LA, Lando HA. Long-term associations of helpful and harmful spousal behaviors with smoking cessation. *Addictive behaviors*. 1996;21(2):173-185.
 48. Mora S, Cook N, Buring JE, Ridker PM, Lee I-M. Physical activity and reduced risk of cardiovascular events potential mediating mechanisms. *Circulation*. 2007;116(19):2110-2118.
 49. de Maat MP, Klufft C. The association between inflammation markers, coronary artery disease and smoking. *Vascular pharmacology*. 2002;39(3):137-139.
 50. Autenrieth C, Schneider A, Doering A, et al. Association between different domains of physical activity and markers of inflammation. *Medicine and science in sports and exercise*. 2009;41(9):1706-1713.
 51. Roohafza HR, Afshar H, Keshteli AH, et al. What's the role of perceived social support and coping styles in depression and anxiety? *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences*. 2014;19(10):944.
 52. Tartavouille TM. A predictive model of the effects of depression, anxiety, stress, 6-minute-walk distance, and social support on health-related quality of life in an adult pulmonary hypertension population. *Clinical nurse specialist*. 2015;29(1):22-28.
 53. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain - immune interactions. *Annals of medicine*. 2003;35(1):2-11.
 54. Tiemeier H, Hofman A, van Tuijl HR, Kiliaan AJ, Meijer J, Breteler MM. Inflammatory proteins and depression in the elderly. *Epidemiology*. 2003;14(1):103-107.
 55. Empana J, Sykes D, Luc G, et al. Contributions of Depressive Mood and Circulating Inflammatory Markers to Coronary Heart Disease in Healthy European Men The Prospective Epidemiological Study of Myocardial Infarction (PRIME). *Circulation*. 2005;111(18):2299-2305.
 56. Toker S, Shirom A, Shapira I, Berliner S, Melamed S. The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *Journal of occupational health psychology*. 2005;10(4):344.
 57. DiNicola G, Julian L, Gregorich SE, Blanc PD, Katz PP. The role of social support in anxiety for persons with COPD. *Journal of psychosomatic research*. 2013;74(2):110-115.

-
58. O'Donovan A, Hughes BM, Slavich GM, et al. Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion–biology relationships. *Brain, behavior, and immunity*. 2010;24(7):1074-1077.