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Subgroup analysis of symptoms and their effect on functioning, exercise capacity, and physical activity in patients with severe chronic obstructive pulmonary disease

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Abstract

Background—Little is known about symptom clusters and their effect on outcomes in people with chronic obstructive pulmonary disease (COPD).

Purposes—To determine whether subgroups of patients with COPD could be identified by symptom ratings, whether they differed on selected demographic and clinical characteristics, and whether they differed on functioning, exercise capacity, and physical activity.

Method—Subjects with severe COPD ($n = 596$) were drawn from the National Emphysema Treatment Trial dataset. Data were drawn from questionnaires and clinical measures.

Results—Two subgroup clusters emerged from four symptoms. Mean age and the proportion of participants with higher education, higher income levels, and using oxygen at rest were significantly different between subgroups. Participants with high levels of symptoms had lower functioning and decreased exercise capacity. Symptom cluster subgroups were significantly associated with social functioning.

Conclusion—These findings suggest that screening for high levels of symptoms may be important in patients with severe COPD.

Keywords

Chronic obstructive pulmonary disease; Functioning; National Emphysema Treatment Trial; Symptoms; Symptom clusters

Introduction

The social burden of chronic obstructive pulmonary disease (COPD) is substantial, and it is projected to be the seventh leading cause of disability-adjusted life years lost worldwide by 2030.¹ COPD is characterized by gradual deterioration in lung function with multiple distressing symptoms that influence functional status and quality of life.^{2,3} It has been

suggested that COPD symptoms have a greater effect on functional limitation than disease severity.⁴ Now symptoms have been included to determine COPD severity in the Global Initiative for Chronic Obstructive Lung Disease.⁵

Previous research focused on single symptoms. However, people with COPD rarely experience a single symptom in isolation. They are more likely to experience multiple symptoms that potentially interact with each other, referred to as a symptom cluster. A symptom cluster is defined as a group of symptoms that are related to each other and occur together.^{6,7} During the past decade, symptom clusters have been examined in people with different chronic diseases including cancer, chronic hepatitis, end stage renal disease, heart failure, and human immunodeficiency virus disease.⁸ However, little is known about symptom clusters and their effect on outcomes in people with COPD.

Symptom clusters

Researchers have used two approaches to examine symptom clusters: (1) grouping symptoms using a factor analysis or cluster analysis and (2) grouping subjects based on differences in the severity of symptoms (i.e. one group with high scores from all symptoms vs. one group with low scores from all symptoms) using a cluster analysis. The second approach was applied to populations with cancer,^{9–14} heart disease,^{15–18} and multiple sclerosis.^{19,20} In these studies, researchers identified distinct subgroups, based on 3–23 symptoms. Grouping subjects based on differences in ratings of symptoms may be more useful clinically because it would allow health care providers to identify subgroups of patients who may be at risk of poorer outcomes. This approach would also enable health care providers to develop symptom management strategies that can be tailored to a specific patient subgroup. Patients in a high-risk group who experience high levels of symptoms may need different types or doses of interventions for symptom relief than patients in a moderate-risk group.¹² However, an examination of the characteristics of patients who reported high levels of symptoms was inconclusive. The demographic and clinical characteristics did not clearly distinguish those who reported low levels of symptoms from those who reported high levels of symptoms.^{9,11–13} To date, no study has examined subgroups of patients with COPD based on their experience with common symptoms or the relationship between symptom clusters, demographic and clinical characteristics.

Symptom clusters in other diseases have been associated with functioning, quality of life, and health status.^{10–12,21} Subgroups with high scores on multiple symptoms had worse functioning, quality of life, and health status.^{10–12,21} In the oncological literature, self-reported functioning was examined as an outcome of symptom clusters.^{9,13} The use of objectively measured exercise capacity as an outcome of symptom clusters would strengthen the science.

In the past literature, single symptoms such as dyspnea or anxiety can influence functioning, exercise capacity, and physical activity in people with COPD.^{4,19,22} But symptoms interact with each other and a cluster of symptoms may be more sensitive to a change in health status than a single symptom. If true in the clinical setting it would be important to assess symptoms as a cluster rather than assessing single symptoms one at a time.

Dyspnea, anxiety, depression, and fatigue in people with COPD

People with COPD experience four symptoms that are highly prevalent and closely related to each other: dyspnea, anxiety, depression, and fatigue. Dyspnea is the most common and disabling symptom.^{2,23} As the disease progresses, patients experience a downward cycle of dyspnea, inactivity, and physical deconditioning, often accompanied by anxiety and depression.²⁴ Research has confirmed that dyspnea is closely related to anxiety and depression in people with COPD.^{25,26} Solano et al²⁷ found that the prevalence of anxiety in people who have recently recovered from an acute exacerbation of COPD ranged between 50% and 57%; the prevalence of depression in people who have recently recovered from an acute exacerbation of COPD ranged between 37 and 71%. Dyspnea and fatigue appear to interact with each other and fatigue is associated with anxious and depressed mood.⁴ Fatigue has been identified as one of the important, disease-related problems that adversely affects the lives of people with COPD.⁴ After dyspnea, the second most prevalent symptom in a study of people with COPD was lack of energy.^{2,23} The prevalence of fatigue was 50–71% in people with COPD.^{2,28} This symptom becomes increasingly prevalent as disease progresses.²⁹

Purposes

The purposes of this study were to determine whether subgroups of patients with COPD could be identified by their ratings of symptoms (i.e. dyspnea, anxiety, depression, and fatigue), whether they differed on selected demographic and clinical characteristics, and whether they differed on functioning, exercise capacity, and physical activity, using data from the National Emphysema Treatment Trial (NETT).

Methods

Design

This cross-sectional secondary analysis used data from the National Emphysema Treatment Trial (NETT). The NETT study's aim was to evaluate the safety and effectiveness of lung volume reduction surgery.³⁰ It was conducted by the Centers for Medicare and Medicaid Services, the National Institutes of Health, and the Agency for Healthcare Research and Quality. The trial's methods have been reported in-depth elsewhere.^{31,32} Briefly, 3777 patients were screened for the NETT from 1998 to 2002 (Fig. 1). Patients were included if they had moderate-to-severe emphysema (FEV1 < 45% predicted, residual volume > 150% predicted), had been non-smokers for at least 6 months, and had completed a pulmonary rehabilitation program before randomization. Exclusion criteria included characteristics that placed patients at risk of perioperative morbidity or mortality, such as, pulmonary hypertension, emphysema unsuitable for lung volume reduction surgery, and medical conditions or other circumstances that precluded a patient from completing the trial. Primary outcomes of the original study were mortality and maximum exercise capacity 2 years after randomization.

Sample, settings, and procedures

All participants at the 17 NETT clinics were randomly assigned to usual medical therapy alone or to usual medical therapy plus lung volume reduction surgery.³² All participants completed 16–20 sessions of pulmonary rehabilitation before randomization, and six sessions of rehabilitation after randomization. For this analysis, we included participants in the medical therapy group. We used baseline data for all study variables, except physical activity. Baseline data were collected prior to rehabilitation and prior to randomization. Data for physical activity were collected one month after randomization. All participants provided written, informed consent, and the institutional review board at each clinic approved the study. This secondary study protocol was approved by the Institutional Committee on Human Research at the primary investigator's hospital.

Instruments

Demographic data—Information about age, gender, marital status, smoking history, race, income, medication use, and current oxygen use were obtained by interview. All questionnaires were administered after clinical measures were performed and study eligibility was determined.

Pulmonary function testing—Pulmonary function tests, including post bronchodilator spirometry and single-breath diffusion capacity, were performed according to American Thoracic Society (ATS) guidelines.^{33,34} Predicted normal values were calculated for spirometry and diffusion capacity.^{35,36} Arterial blood gas results for participants at rest breathing room air were used: partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide (PaCO_2).

Symptoms

Dyspnea: Dyspnea was measured by the University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ). This 24-item instrument measures shortness of breath for 21 daily activities and the limitations it causes in daily life. Twenty-one questions address daily activities; three address limitations. The former were used to assess the level of dyspnea for this study. Participants were asked to answer the 21 questions on a scale of 0 (none at all) to 5 (maximal or unable to do because of breathlessness). Scores ranged from 0 (best) to 105 (worst). Internal consistency for the UCSD-SOBQ ($\alpha = .96$) has been previously reported.³⁷ Concurrent validity of the instrument is supported by strong correlations with FEV1 ($r = -.50$) and the 6-minutewalk test (6MWT) ($r = -.68$).³⁷ Internal consistency for our study was Cronbach's $\alpha = .94$.

Anxiety: The State-Trait Anxiety Inventory (STAI) was used to elicit the participants' experience of anxiety. The state anxiety was used for this study. It comprises 20 questions. Subjects reported how they felt at that moment using a scale of 1 (not at all), 2 (some-what), 3 (moderately so), and 4 (very much so).³⁸ Possible scores range from 20 to 80, with the higher scores indicating increased state anxiety. Test-retest reliability ranged from .16 to .54.³⁸ This scale correlates highly with other measures of anxiety ($r = .80$).³⁸

Depression: The Beck Depression Inventory (BDI) was used to describe depression. This instrument comprises 21 items: 13 assess cognitive-mood symptoms and 8 assess physical-performance symptoms of depression.³⁹ Participants were asked to answer how they felt over the past 2 weeks. Possible scores range from 0 to 63 and higher scores reflect greater depression. Test–retest reliability ($r = .95$) has been reported.⁴⁰ In a factor loading, the BDI and Center for Epidemiologic Studies Depression Scale loaded into the same group.⁴¹ Internal consistency for this study was Cronbach’s $\alpha = .70$.

Fatigue: The Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-36) was used to assess fatigue. Participants were asked to respond to the question, “Did you feel tired?” during the past 4 weeks on a scale of 1 (all the time) to 6 (none of the time).

Functioning—Functioning was also measured with the MOS-36. This instrument consists of 36 items that measure eight distinct dimensions of health: physical-functioning, role-physical, bodily pain, general health perception, vitality, social functioning, role-emotional, and mental health. The physical functioning, social functioning, and general health perception subscales were used for the current analysis. A higher score indicates better health. Scores for each subscale can range from 0 to 100. Reliability coefficients of the MOS-36 ranged from .65 to .94.⁴² McHorney et al⁴³ compared MOS-36 scores across a population with serious medical conditions, minor medical conditions, and psychiatric problems and found that MOS-36 scores were significantly different among groups. Internal consistency for the physical and social functioning subscales in the current study was Cronbach’s $\alpha = .84$ and $.80$, respectively.

Exercise capacity—Exercise capacity was measured as the peak workload on a graded exercise test. The test was performed on an electromagnetically-braked cycle ergometer, and load was increased at a rate of 5 or 10 W every minute while participants breathed 30% oxygen. Participants were informed when the cadence fell below 40–70 revolutions/min (rpm), and every minute they were coached to maintain speed. The test was terminated when the cadence dropped below 40 rpm and did not return. Adequate test–retest reliability of oxygen uptake during a cycle ergometer test has been reported in people with COPD (reliability coefficient = .97).⁴⁴

The 6MWT was also used to assess exercise capacity. Participants were rested for 10 min before starting the test. They were allowed to have prescribed oxygen during the test. Heart rate and oxygen saturation were measured with a pulse oximeter before and after each walk test. Course layout and length varied by the participating institution. Maximum distance walked was used for the analysis. Intraclass correlation coefficient between two 6MWTs was .88.⁴⁵ The validity of the 6MWT was supported by strong correlations with oxygen consumption using a peak exercise test ($r = .51$).⁴⁶

Physical activity—To evaluate physical activity, participants were asked how many days during the previous week they performed lower extremity endurance exercises and for how many minutes each day. They were asked to specify the actual number of days and minutes of exercise. The physical activity data were collected by telephone interview at one month after randomization. At this point subjects had completed pulmonary rehabilitation prior to

randomization and most of subjects had pulmonary rehabilitation after randomization at the time when physical activity data were collected. However, there is substantial evidence suggesting that pulmonary rehabilitation does not change the volume of physical activity.^{47,48}

Data analysis

All data were analyzed with SPSS 20.0. All continuous variables were expressed as mean and standard deviation. Categorical variables were presented as percentage and frequency. Descriptive statistics were used to describe sample characteristics.

Scores (for dyspnea, anxiety, depression, and fatigue) from the UCSD-SOBQ, STAI, BDI, and MOS-36 were standardized on their ranges and then used in the cluster analysis to equalize the influence of variables with different scale lengths on the cluster solution. An agglomerative hierarchical cluster analysis was performed with squared Euclidean distances used in the proximities matrix and weighted average linkage used as the clustering method. Of the two approaches in hierarchical cluster analysis, we chose the agglomerative method that joins smaller clusters into bigger clusters. Squared Euclidean distances were used as a measure of dissimilarity. Weighted average linkage method was chosen because it helps to identify subgroups with different sample sizes.⁴⁹ The appropriate number of cluster solutions was determined by dendograms, incremental changes in agglomeration coefficients,⁵⁰ and the expert judgment of researchers.

A *t*-test or chi-square test was used to determine whether significant differences existed among the subgroups of participants in demographic and clinical characteristics, symptom scores, and outcome measures.

Hierarchical multiple regressions were used to examine the effect of symptom clusters and single symptoms (i.e., dyspnea, anxiety, depression, and fatigue) on functioning and exercise capacity. First, demographic and clinical characteristics were entered into a hierarchical regression model to predict outcome variables. The characteristics were selected from a Pearson correlation coefficient analysis. In the second step of analysis, subgroup variables (symptom clusters) and single symptoms were added to the regression model separately to examine the independent contribution of symptoms on functioning and exercise capacity. To be consistent, single symptoms were changed to binary variables like the symptom cluster subgroup variables, which are binary (Subgroup 1 vs. Subgroup 2). As a cutpoint for binary variables for each symptom, we chose the symptom score that 83% of the sample achieved because the sample number in Subgroup 1 was 83% of the total sample. A $p < .05$ was considered statistically significant.

Results

Cluster analysis

Two, three, and four cluster solutions were examined in cluster analysis. We found two distinctive clusters, based on four symptoms. With the two-cluster solution 82.9% of the sample ($n = 494$) was categorized in the “all low” subgroup (Subgroup 1) and 17.1% ($n = 102$) in the “all high” subgroup (Subgroup 2).

Differences in symptom scores

Standardized symptom scores are shown for each subgroup in Fig. 2, illustrating the relatively high level of symptom scores in Subgroup 2 compared with Subgroup 1. Table 1 presents symptom scores for the two subgroups. Participants in Subgroup 2 had worse dyspnea, anxiety, depression, and fatigue than those in Subgroup 1.

Differences in demographic and clinical characteristics

Of the demographic and clinical characteristics, mean age and the proportion of participants with higher education, higher income levels, and using oxygen at rest were significantly different between subgroups (Table 2). No significant differences were found in the other study variables between subgroups.

Symptoms and outcomes

Significant differences between subgroups were found in the MOS-36 scores for physical functioning, social functioning, and general health subscales (Table 3). Participants in Subgroup 2 showed lower scores in physical functioning, social functioning, and general health subscales than those in Subgroup 1. Significant differences were found in peak workload between subgroups (Table 3). Participants in Subgroup 1 had better exercise capacity than those in Subgroup 2. Significant subgroup differences were found in the 6-minutewalking distance (Table 3). Results show that participants in Subgroup 1 walked a longer distance than those in Subgroup 2. No significant subgroup differences were found for the time spent in low extremity endurance physical activity between subgroups (Table 3).

Age, gender, FEV1% predicted, education level, and income level explained 4.4% of the total variance in physical functioning, 15.4% in social functioning, and 3.8% in general health (Table 4). When symptoms were added to the model, the largest change in total variance in physical functioning was attributed to dyspnea. The largest change in total variance in social functioning was explained by symptom cluster subgroup variable. The largest change in total variance in general health was explained by depression (Table 4).

Age, gender, FEV1% predicted, education level, and income level explained 34% of the total variance in peak workload on the cycle ergometer and 16.5% in 6-minute walk distance (Table 5). When symptoms were added to the model, the largest change in total variance in peak workload on cycle ergometer and 6-minute walk distance was explained by dyspnea (Table 5).

Discussion

To our knowledge, this is the first study to attempt to identify subgroups based on symptom ratings in people with COPD. Cluster analysis identified two distinct subgroups of subjects. Those who reported high levels of four symptoms had poorer exercise capacity, poorer physical and social functioning, and poorer general health, but no difference was noted in disease severity as measured by blood gases and lung function tests. Differences were

observed in age, education, income level, and the use of supplemental oxygen at rest. Symptom cluster subgroups were significantly associated with social functioning.

Subjects in Subgroup 1 who had less symptom burden were older than those in Subgroup 2, which is consistent with research on cancer patients.⁹ Also, Cleland et al⁵¹ found that people aged 60 and older had less anxiety and depression than younger people. It is surprising that severity of disease was not significantly different for the two groups of people. None of the measures of disease severity were different including airflow obstruction, diffusion capacity, and resting arterial blood gases. This illustrates the importance of assessing symptoms to monitor the progression of disease. It is also consistent with recent changes in the GOLD staging of COPD. The observed difference in the use of supplemental oxygen at rest is indicative of progressive disease. The observed significant difference in education raises questions about the potential effects of health literacy.^{52,53} The group with the greatest symptom burden also had less education; the lower education level places them at risk of problems with health literacy. If patients do not understand what health care providers teach them about COPD, they may be less effective in managing their symptoms. This could contribute to their symptom burden. Difference in income level is understandable when one considers that people in Subgroup 1 were highly educated. Low income level should also concern health care provider: People with low economic status might not get timely care for symptom management for several reasons such as lack of insurance.

Surprisingly, few demographic and clinical characteristics distinguished the two subgroups. This is consistent with the findings of oncology studies,^{9,11–13} even though their population and the set of symptoms examined to form a cluster were different. Few demographic and clinical characteristics, such as age⁹ and employment status,¹³ were significantly different among subgroups. Perhaps the lack of significant differences in clinical characteristics may be due to relatively homogenous group membership, in terms of the level of severity of disease. Most of our participants had severe COPD. Further study is warranted with a more heterogeneous group of people with COPD.

In this study, participants in Subgroup 2 had worse physical and social functioning and poorer general health compared to the Subgroup 1. These findings are consistent with work in oncology that found that symptom clusters had an adverse effect on functioning.^{9,13} It has been reported that symptoms may play an important role in patient functioning. Isolated symptoms of dyspnea,^{4,54} anxiety,⁴ depression,⁵⁴ and fatigue⁴ have been associated with reduced functioning in people with COPD. Thus, it is not surprising that high levels of all four symptoms were associated with a negative effect on functioning. In this study, symptom clusters especially were significantly associated with social functioning when compared with single symptoms. This finding confirms that not only is a high level of a single symptom associated with functioning, but a cluster of high levels of symptoms is also associated with functioning in people with COPD.

Although we found significant differences in peak workload and 6-minute walk distance between Subgroups 1 and 2, these differences could not be considered clinically important. In past studies, it has been reported that isolated symptoms were negatively associated with exercise capacity in people with COPD. The symptom of dyspnea was negatively associated

with exercise capacity, as measured by the 12-minute walk test.⁵⁵ Anxiety was associated with reduced exercise capacity, 6-minute walk distance.²² Physical fatigue was negatively related to maximal exercise performance.⁵⁶ Our findings confirmed that exercise capacity decreases as the levels of all four symptoms (dyspnea, anxiety, depression, and fatigue) increase in people with COPD. This suggests that clusters of high levels of symptoms were not only related to self-reported impaired functioning in daily life but also associated with a greater effect on physical functioning. However, symptom cluster subgroups were associated with exercise capacity less than a single symptom like dyspnea. The theory of unpleasant symptoms⁵⁷ suggests that multiple symptoms or symptom clusters have a multiplicative rather than an additive effect on outcomes. It emphasizes the importance of multiple symptoms and the interaction between symptoms. Our findings showed that a single symptom was more associated with certain outcomes. This finding should be examined further in people with COPD because we arbitrarily made binary variables for each symptom but were unable to do so in the same way that symptom cluster subgroups were created in this study through cluster analysis.

In the COPD literature, dyspnea has been strongly associated with physical activity.^{58–61} In populations with multiple sclerosis,^{19,20} symptom clusters have been negatively associated with physical activity, which was measured by ActiGraph. However, our study did not show significant differences in the level of physical activity among subgroups based on symptom ratings. This may be due to the instrument that was used to measure the level of physical activity. In this study, the duration of physical activity was asked through interview. Further study may be needed to examine the relationship between objectively measured physical activity and symptom clusters in people with COPD. Participants had undergone pulmonary rehabilitation before randomization and continued pulmonary rehabilitation after randomization, which might have affected the level of physical activity in this population. Longer periods of pulmonary rehabilitation produce greater sustained benefits than shorter programs.⁶² Accordingly, we compared the number of rehabilitation exercise sessions and education sessions attended prior to randomization among two subgroups; no significant differences were found. We also compared proportion of subjects who continued pulmonary rehabilitation after randomization at the time when physical activity data were collected; no significant difference was found.

This study is based on data from a well-designed, randomized controlled trial, an obvious strength. However, the study also has its limitations. First, data were collected from people with very severe COPD. Thus, the results cannot be generalized to patients with milder COPD. Second, the fact that we used one item to assess fatigue may affect our findings. Future studies, using more structured instruments, are needed to confirm these findings. Third, using instruments that measure different dimensions of symptoms (intensity vs. frequency) may have affected our findings. Instruments, measuring same aspects of symptoms, should be used in future studies. Fourth, data for physical activity were collected after randomization in the NETT study. Participants in the medical care group might have been disappointed that they were not chosen for the surgery group. This might have affected their level of physical activity.

Conclusion

Two distinct subgroup clusters emerged based on four symptom ratings. Those subjects who had high levels of symptoms had worse functioning and exercise capacity than those who had low levels of symptoms. Symptom cluster subgroups were significantly associated with social functioning. These findings suggest that screening for high levels of symptoms may be important in patients with severe COPD. This research also shows the importance of evaluating the combined symptom load as a cluster rather than individual symptoms in isolation for certain health-related outcomes. This study provides empirical evidence that symptom clusters and their associated outcomes in people with COPD merit further investigation. This has potential implications for interventions; targeting combinations of symptoms rather than individual symptoms may be more effective in improving social functioning in people with COPD. Further study is warranted to examine subgroup analysis in a more heterogeneous population with COPD and to compare the magnitude of contribution of symptom cluster subgroups and single symptoms to other health-related outcomes.

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Fig. 1.
Flow chart for study sample.

Fig. 2.
Standardized symptom scores for the two subgroups.

Table 1

Symptom scores for all sample and subgroups formed with two cluster solutions.

Symptom Inventory (possible score range)	All sample (<i>N</i> = 596)	Subgroup 1	Subgroup 2
		All low (<i>n</i> = 494, 82.9%)	All high (<i>n</i> = 102, 17.1%)
		Mean ± SD	Mean ± SD
Dyspnea score in UCSD (0–105)	58.40 ± 16.51	55.32 ± 15.84 [*]	73.31 ± 10.49
STAI score (20–80)	34.50 ± 10.46	32.05 ± 8.74 [*]	46.38 ± 10.01
BDI score (0–63)	9.34 ± 5.91	8.07 ± 5.14 [*]	15.47 ± 5.57
Fatigue score in MOS-36 (1–6)	3.81 ± 1.23	4.15 ± 1.01 [*]	2.13 ± .67

UCSD, University of California, San Diego Shortness of Breath Questionnaire; STAI, Spielberger State Trait Anxiety Inventory; BDI, Beck Depression Inventory; MOS-36, Medical Outcomes Study 36-Item Short Form Health Survey.

Higher score in UCSD, STAI, and BDI means more dyspneic, anxious, and depressive. Lower score in MOS-36 means more fatigued.

^{*}
p < .05.

Table 2

Demographic and clinical characteristics for the total sample and differences in demographic and clinical characteristics among two subgroups.

	All sample (N = 596)	Subgroup 1	Subgroup 2
		All low (n = 494, 82.9%)	All high (n = 102, 17.1%)
	Mean ± SD	Mean ± SD	Mean ± SD
	n (%)	n (%)	n (%)
Age (years)	65.93 ± 10.21	66.36 ± 9.64 [*]	63.82 ± 12.45
Male	379 (63.6%)	320 (64.8%)	59 (57.8%)
White	561 (94.1%)	463 (93.7%)	98 (17.5%)
Married	385 (64.6%)	323 (65.4%)	62 (60.8%)
College degree or higher	303 (50.8%)	264 (87.1%) [*]	39 (12.9%)
Income (\$30,000 or more)	283 (47.6%)	247 (50.0%) [*]	36 (35.6%)
Cigarette smoking, pack years	66.52 ± 33.02	65.40 ± 31.48	71.90 ± 39.33
Oxygen use at rest	307 (51.5%)	242 (49.0%) [*]	65 (63.7%)
Oxygen use during sleeping	392 (65.8%)	316 (64.0%)	76 (74.5%)
Use of oral corticosteroids	170 (28.5%)	142 (28.7%)	28 (16.5%)
Use of inhaled corticosteroids	424 (71.1%)	351 (71.1%)	73 (71.6%)
FEV1 (% predicted)	27.06 ± 7.10	27.02 ± 7.03	27.26 ± 7.46
FVC (% predicted)	67.49 ± 15.79	67.70 ± 15.72	66.49 ± 16.19
FEV1/FVC	.32 ± .06	.32 ± .06	.32 ± .07
DLCO (% predicted)	28.47 ± 9.83	28.53 ± 9.65	28.21 ± 10.70
PaO ₂	64.57 ± 10.16	64.59 ± 10.06	64.51 ± 10.70
PaCO ₂	42.55 ± 5.27	42.52 ± 5.25	42.72 ± 5.34
Pulmonary rehabilitation prior to randomization; exercise session attended	20.78 ± 3.24	20.72 ± 3.23	20.96 ± 2.89
Pulmonary rehabilitation prior to randomization; education session attended	19.73 ± 2.67	19.70 ± 2.56	19.83 ± 3.13
Number of subjects who continued pulmonary rehabilitation after randomization ^a	539 (96.1%)	452 (96.6%)	87 (93.5%)

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusion capacity of carbon monoxide; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood.

* $p < .05$ for t -test or chi-square test.

^a At the time when physical activity data were collected.

Table 3

Outcome variables for the total sample and differences in outcome variables among two subgroups.

Outcome variable (possible score range)	All sample (N = 596)	Subgroup 1	Subgroup 2
		All low (n = 494, 82.9%)	All high (n = 102, 17.1%)
	Mean ± SD	Mean ± SD	Mean ± SD
Physical functioning in MOS-36 (0–100)	21.40 ± 16.64	23.03 ± 16.28*	13.53 ± 16.16
Social functioning in MOS-36 (0–100)	60.86 ± 27.60	65.26 ± 26.13*	39.58 ± 24.51
General health in MOS-36 (0–100)	37.63 ± 19.49	40.26 ± 19.47*	27.85 ± 13.71
Peak workload on cycle ergometer (watt)	36.01 ± 20.88	37.26 ± 20.86*	29.89 ± 19.98
6 min walk distance (feet)	1100.99 ± 306.00	1122.89 ± 301.16*	992.16 ± 308.11
Time spent for lower extremity physical activity (min)	106.42 ± 69.11	108.05 ± 67.97	98.21 ± 74.43

MOS-36; Medical Outcomes Study 36-Item Short Form Health Survey.

Higher score in MOS-36 means better functioning and general health.

*
p < .05.

Table 4

Results from hierarchical regression models predicting functioning and general health in MOS-36 ($N = 596$).

Predictors	Physical functioning in MOS-36			Social functioning in MOS-36			General health in MOS-36		
	R^2	R^2 change	Beta	R^2	R^2 change	Beta	R^2	R^2 change	Beta
Step 1 ^a	.044*			.154*			.038*		
Step 2: symptom cluster subgroup	.091*	.047*	-.9.70*	.144*	.121*	-25.82*	.119*	.081*	-14.96*
<i>F</i> equation	$F_{6,587} = 9.78, p = .0001$			$F_{6,588} = 16.50, p = .0001$			$F_{6,588} = 13.26, p = .0001$		
Step 2: dyspnea	.127*	.083*	-12.61*	.128*	.104*	-22.58*	.074*	.035*	-13.68*
<i>F</i> equation	$F_{6,587} = 14.19, p = .0001$			$F_{6,588} = 14.39, p = .0001$			$F_{6,588} = 7.79, p = .0001$		
Step 2: anxiety	.058*	.014*	-5.19*	.112*	.088*	-16.77*	.065*	.027*	-8.45*
<i>F</i> equation	$F_{6,587} = 6.82, p = .0001$			$F_{6,588} = 12.33, p = .0001$			$F_{6,588} = 6.81, p = .0001$		
Step 2: depression	.063*	.019*	-5.64*	.139*	.115*	-19.05*	.124*	.086*	-14.16*
<i>F</i> equation	$F_{6,587} = 6.56, p = .0001$			$F_{6,588} = 13.83, p = .0001$			$F_{6,588} = 13.92, p = .0001$		
Step 2: fatigue	.065*	.021*	-15.03*	.124*	.100*	-18.26*	.051*	.013*	-13.58*
<i>F</i> equation	$F_{6,587} = 16.50, p = .0001$			$F_{6,587} = 9.78, p = .0001$			$F_{6,588} = 5.24, p = .0001$		

All models in step 2 were analyzed separately.

FEV1, forced expiratory volume in 1 s; MOS-36, Medical Outcomes Study 36-Item Short Form Health Survey.

* p value < .05.

^a Predictors in step 1 include age, gender, FEV1% predicted, education level, and economic status.

Table 5

Results from hierarchical regression models predicting exercise capacity ($N = 596$).

Predictors	Peak workload on cycle ergometer (watt)			6-minute walk distance (feet)		
	R^2	R^2 change	Beta	R^2	R^2 change	Beta
Step 1 ^a	.340 [*]			.165 [*]		
Step 2: symptom cluster subgroups	.353 [*]	.014 [*]	−6.66 [*]	.191 [*]	.025 [*]	−132.68 [*]
<i>F</i> equation	$F_{6,575} = 52.40, p = .0001$			$F_{6,577} = 22.69, p = .0001$		
Step 2: dyspnea	.376 [*]	.036 [*]	−8.13 [*]	.212 [*]	.046 [*]	−134.51 [*]
<i>F</i> equation	$F_{6,575} = 57.68, p = .0001$			$F_{6,577} = 25.81, p = .0001$		
Step 2: anxiety	.344 [*]	.005 [*]	−2.91 [*]	.178 [*]	.013 [*]	−71.32 [*]
<i>F</i> equation	$F_{6,575} = 50.30, p = .0001$			$F_{6,577} = 21.25, p = .0001$		
Step 2: depression	.342	.002	−2.08	.181 [*]	.016 [*]	−77.37 [*]
<i>F</i> equation	$F_{6,575} = 49.81, p = .0001$			$F_{6,577} = 20.89, p = .0001$		
Step 2: fatigue	.351 [*]	.011 [*]	−4.58 [*]	.176 [*]	.011 [*]	−66.19 [*]
<i>F</i> equation	$F_{6,575} = 51.72, p = .0001$			$F_{6,577} = 20.55, p = .0001$		

All models in step 2 were analyzed separately.

FEV1, forced expiratory volume in 1 s; MOS-36, Medical Outcomes Study 36-Item Short Form Health Survey.

* p value < .05.

^a Predictors in step 1 include age, gender, FEV1% predicted, education level, and economic status.