ERJ Express. Published on January 14, 2010 as doi: 10.1183/09031936.00021409

Impact of Changes in Physical Activity on Health-Related Quality of Life among Patients with Chronic Obstructive Pulmonary Disease

Authors: Cristóbal Esteban MD, José M. Quintana PhD, Myriam Aburto PhD, Javier Moraza MD, Mikel Egurrola MD, Julio Pérez-Izquierdo MD, Susana Aizpiri MD, Aguirre Urko MSc, Alberto Capelastegui PhD.

From the Pneumology Department (C. Esteban, M. Aburto, J. Moraza, M. Egurrola, J. Pérez-Izquierdo, S. Aizpiri, A. Capelastegui) and Unidad de Investigación - CIBER Epidemiología y Salud Pública (CIBERESP) (J.M. Quintana, U. Aguirre), Hospital Galdakao-Usansolo, Galdakao, Bizkaia, Spain.

Correspondence and requests for reprints should be addressed to:

Cristóbal Esteban, MD.
Servicio de Neumología
Hospital de Galdakao-Usansolo
Barrio Labeaga s/n. 48960
Galdakao, Bizkaia, Spain.
Telephone number +34-944007002, Fax: +34-94 400 7132
e-mail: cristobal_esteban@yahoo.es

Keywords: Pulmonary Disease, Chronic Obstructive; Physical Activity; Quality of Life.

Running title: COPD: Physical Activity and Quality of Life.

Abstract word count: 200.

Manuscript word count: 3888.

Abstract

To evaluate whether changes in regular physical activity (PA) affect health-related quality of life (HRQoL) among patients with chronic obstructive pulmonary disease (COPD).

611 patients (mean age 67.2 ± 8.4; FEV1 49.7 ± 14.6) completed the Saint George's Respiratory Questionnaire (SGRQ), the Chronic Respiratory Questionnaire (CRQ), and the Medical Outcomes Study Short Form (SF-36) questionnaire. Physical activity, defined as patients' self-reported regular walking times, was classified as low, moderate, and high. After 5 years, 391 survivors again completed these instruments.

After adjustment for relevant confounders, patients who reported low PA at baseline and who increased their PA over the study period improved their SGRQ and CRQ scores by 15.9 and 8.7 points respectively. Patients who moved from moderate to high PA improved their SGRQ scores by 18.4 and their CRQ scores by 14.8. Slightly smaller increases were observed for patients who maintained a high level of PA throughout the study period. Maintaining a low level of PA or decreasing PA over the study period was associated with a significant HRQoL decline.

Among COPD patients, a reduction in time spent engaging in PA or maintaining a low level may impair HRQoL, whereas an increase in PA can improve HRQoL parameters.

INTRODUCTION

Regular physical activity (PA) has been shown to be beneficial in the general population for the primary and secondary prevention of cardiovascular disease, hypertension, type 2 diabetes mellitus, obesity, osteoporosis, and some kinds of cancer [1]. Physical activity is associated with reduced mortality [2] .These benefits apply to men and women, young and old [3]. Extreme levels of fitness are not required—engaging in a moderate-intensity physical activity on most days of the week is generally sufficient [4]. Walking, an activity that most people can do, has been associated with virtually all of the benefits of regular physical activity [5].

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airway obstruction that worsens over time. Although its primary impact is on the lungs, it also produces biochemical, structural, and functional alterations throughout the body [6,7]. These respiratory and systemic changes cause a progressive decline in health [8].

Quality of life is an important measure of health, particularly for older people and those suffering from a chronic disease. It is thus important to use health-related quality of life (HRQoL) tools that can evaluate the repercussions of a disease such as COPD on the entire patient. In patients with COPD, poor HRQoL has been associated with an increased likelihood of hospitalization [9], hospital readmission [10], and mortality [11].

Data from cross-sectional studies show a direct association between HRQoL and PA in general population, but the data are scarce and incomplete [12]. Even less information is available about this relationship among patients with COPD. As suggested by a population-based study, regular physical activity may counter the

decline in HRQoL in part by reducing COPD-related hospital admissions and mortality and slowing the decline in FEV_1 [13, 14].

We designed this study to determine the impact of changes in the level of PA, primarily low-intensity walking during leisure time, on HRQoL in a cohort of patients with COPD over a 5-year period.

METHODS

Subjects

We recruited patients being treated for COPD at the outpatient clinics of Hospital Galdakao-Usansolo between February 1998 and February 1999. Hospital Galdakao-Usansolo is a 400-bed teaching hospital in the Basque Country (northern Spain) that serves a population of 300,000 inhabitants. It belongs to the network of public hospitals of the Basque Health Care Service, which provides free unrestricted care to nearly 100% of the population. A respiratory rehabilitation program was instituted in January 2008.

Consecutive patients were included in the study if they had been diagnosed with COPD for at least six months and had been receiving medical care at one of the hospital's outpatient facilities for at least six months. COPD had to be stable (no increase in respiratory symptoms or changes in treatment) for six weeks prior to enrollment. Other inclusion criteria were forced expiratory volume in one second (FEV_1) <80% of the predicted value, FEV_1/forced vital capacity (FVC) quotient <70%, and a negative bronchodilation test with FEV_1 change <200 mL and under 15% of the baseline value. The functional parameters used were those obtained following bronchodilation. Patients were not eligible for the study if they had been diagnosed with asthma, had extensive pulmonary tuberculosis or neoplastic processes, were suffering from psychiatric or neurological problems that might prevent effective collaboration, or had hearing or other problems that impeded accurate communication. Patients were also excluded if they had participated in a respiratory rehabilitation program. Each patient was given detailed information about the study and provided verbal informed consent to take part in it. The study protocol was approved by the research committee of the Hospital Galdakao-Usansolo.

Study protocol

Patients who fulfilled the selection criteria were interviewed and underwent physical examination soon after recruitment. Spirometry was conducted following criteria from the Spanish Pneumology and Thoracic Surgery Society (SEPAR) [15] with a Master-Scope-PC spirometer (Erich Jaeger GmbH & Co, KG, Wuerzburg, Germany). Theoretical values were those established by the European Community for Steel and Coal [16].

HRQoL was assessed at baseline using 3 instruments: the generic 36-item Medical Outcomes Study Short Form (SF-36), including its physical component summary scale (PCSS) and mental component summary scale (MCSS) [17], and 2 disease-specific questionnaires—the St. George's Respiratory Questionnaire (SGRQ) [18] and the Chronic Respiratory Questionnaire (CRQ) [19]. We used versions of all three instruments that have been validated in Spanish populations [20-22].

Normalized SF-36 values can be estimated to provide a reference value from the general population. To do this, each SF-36 component score is first standardized by using the mean and standard deviations (SD) obtained from a Spanish population of men over age 45 years and then transformed to norm-based (mean=50, SD=10) scoring [23].

At the baseline personal interview, patients were asked about the kinds of physical activities they did. Special emphasis was placed on walking, with questions about time spent walking and distance covered, as has been done in previous studies [24]. The level of physical activity was defined as the time patients spent walking during

their leisure time, and was classified into three categories: low (engaging in light physical activity such as walking for less than 2 hours/week), moderate (engaging in light physical activity such as walking for 2-4 hours/week), and high (engaging in light physical activity such as walking for more than 4 hours/week), again as was done in previous studies [13,25-27]. Comorbidities were determined by reviewing patients' medical records for their clinical histories.

Patients were followed for up to 5 years. During this period, they continued to meet with their primary care physicians and respiratory specialists, and followed the recommendations and prescribed treatments. As is standard practice in our COPD clinics, all patients were urged to stop smoking, if necessary, and to engage in regular physical activity. Primary care physicians, respiratory specialists, and other health-care providers did not provide any interventions related to this study, and the research team did not intervene in patients' routine treatment or in the treatment of exacerbations.

Five years after enrollment, the survivors were again interviewed, underwent spirometry, and completed the 3 HRQoL questionnaires. As before, each was asked about the average time and distance they walked per day. Follow-up interviews were scheduled at outpatient clinics of our hospital during times when patients were clinically stable. Patients who developed a disease that could alter HRQoL or prevent them from completing the HRQoL questionnaires (cancer, Alzheimer's disease, etc.), and those who could not be interviewed personally, as well as those who were enrolled in a pulmonary rehabilitation program during the follow-up period, were excluded from the study.

Vital status was determined by reviewing medical reports and examining the hospital database and public death registries. Deaths were considered confirmed if the record matched the subject on name, sex, and date of birth. The cause of death in all cases was based on hospital reports and public death registries. For deaths that occurred out of the hospital, the researchers telephoned relatives and the primary care physician. The research team analyzed all data and established the causes of death.

Statistical analysis

We present means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

For the comparison of survivors and nonsurvivors, we used the Chi-square and Fisher's exact tests to evaluate associations among categorical variables, and the Student t test for continuous variables. Non-parametric test were used when appropriate.

To evaluate possible correlations between the three levels of physical activity at baseline and sociodemographic and clinical variables and the SF-36, SGRQ, and CRQ, we used the analysis of variance (ANOVA) test with the Scheffeé test for multiple comparisons and the non-parametric Kruskal-Wallis test. The same test was used to check for correlations among the changes in PA over the 5-year study.

We also present graphically the changes in PA over the study period, taking as a reference the normative data of the general population of the same age and gender.

We performed multivariate analysis by means of two generalized linear models. The dependent variables were, respectively, the change in SGRQ scores over the study period and the change in CRQ scores. The main independent variable was the change in PA during the study (PA categories at 5 years vs PA categories at basal time) adjusted by age, FEV_1, previous hospital admissions, level of dyspnea, comorbidities, and mental health status (measured by the SF-36 MCSS) at baseline, and by baseline HRQoL as measured by SGRQ or CRQ scores, respectively, in each corresponding model.

All effects were considered significant at $p<0.05$ unless otherwise noted. All statistical analyses were performed using SAS for Windows statistical software, version 8.2 (SAS Institute, Inc., Carey, NC).

RESULTS

A total of 611 patients fulfilled the study criteria and completed the baseline questionnaires.

After 5 years of follow-up, 445 patients (72.8%) were still alive. Causes of death included exacerbations of COPD (81), other respiratory causes (16), cardiovascular or cerebrovascular disease (40), and other causes (26), mainly various neoplasms; no clear cause of death was recorded for 3 patients (sudden death). Differences between survivors and those who died are shown in Table 1.

Among the 445 survivors, 54 patients were not included in the final analysis: 25 had active neoplasms, 19 had moved out of the area, 7 had developed psychiatric disorders or Alzheimer's disease, 1 became blind, and 2 could not be located. The characteristics of these 54 patients were not different in level of PA or $FEV_{1\%}$, dyspnea, smoking habits, comorbidities, or HRQoL from the 391 survivors.

At baseline, patients who reported lower levels of PA had more dyspnea, were more likely to have been admitted to the hospital for an exacerbation of COPD in the 2 years prior to enrollment, had more comorbidities, and had lower FEV_1 than those with moderate or high levels of PA. There were no significant differences in the other variables between the three PA groups (Table 2).

A number of differences in HRQoL were observed across PA categories. At baseline, there were statistically significant differences in SGRQ scores across the three PA categories in most areas. Differences in CRQ scores were observed mainly between the low PA and high PA groups. With regard to SF-36 scores, differences were

generally observed between the low PA category and the two higher categories (Table 3). Statistically significant differences between the three groups were observed in the “Physical Functioning” area.

After 5 years of follow-up, 254 patients reported the same level of PA that they had reported at baseline, 75 reported less PA, and 62 reported increased PA. At this time, the total SGRQ for the cohort was 38.7 ± 20.8 and the total CRQ was 100.7 ± 27.4. The distribution of the changes in PA is reflected in Table 4. In general, maintaining a low level of PA or decreasing PA over the study period was associated with a statistically significant decline in HRQoL, as measured by the SGRQ and CRQ, while maintaining a high level of PA or increasing PA was associated with an improvement in HRQoL, with greater increases in SGRQ than CRQ scores. In the SF-36 PCSS, a decline was observed across all categories of PA, with the largest changes among patients who reported a lower PA level after 5 years of follow-up. In the MCSS, there was a decline in HRQoL among patients with low PA at baseline and after 5 years of follow-up as well as in those who reported a moderate level of PA at baseline and a low level after 5 years (Table 4).

Changes in PA over the study period, taking as a reference the normative data of the general population of the same age and gender, showed that those who improved their PA over the course of the 5-year follow-up period preserved their SF-36 PCSS values and slightly improved their MCSS. In general, though, they did not reach the levels observed for the general population (Figure 1).

Multivariate analysis of two different models used the total SGRQ score (Model 1) and the total CRQ score (Model 2) as separate dependent variables, and changes in

the reported level of PA over the 5-year study period as the main independent variable (Table 5). Changes in the self-reported level of PA over the course of the study were independently associated with changes in HRQoL in the two models. Using the patients who reported high levels of PA at baseline and after 5 years (High/High) as a reference group, patients who reported low levels of PA at baseline and after 5 years (Low/Low) experienced a decline in HRQoL (an increase of 16.9 units in the total SGRQ score). A similar decline was observed among patients who reported a decline in PA after 5 years of follow-up (Moderate/Low and High/Moderate-Low). When patients in the lowest category of baseline and 5-year PA (Low/Low) were used as a reference group, improvements in HRQoL as measured by decreases in SGRQ scores were observed among patients who increased their PA from baseline or who maintained moderate or high levels of PA (Table 5). Those patients whose changed their PA level from low to moderate/ high had almost 16 less points in the SGRQ than those who maintain their PA as low at 5 years. Maintaining for 5 years the PA level as moderate improved the SGRQ score in 10 units and changing from moderate to high o maintaining at high level improved in more than 16 unit the total domain of the SGRQ with respects to that patients who stayed at low PA level during the study. The magnitude of the improvement in HRQoL was similar regardless of the baseline level of PA. Other variables evaluated, such as BMI and pack-years of cigarettes, did not influence the change in HRQoL. While the mean number of comorbidities increased from 1.7 at baseline to 1.9 after 5 years of follow-up ($p<0.01$), this did not have a significant impact in the multivariate analysis.

DISCUSSION

Among patients with COPD who were not participating in a structured respiratory rehabilitation program, changes in the level of leisure-time PA as measured by the average time spent walking each day was strongly associated with HRQoL. Patients who engaged in low levels of PA over the 5-year study period and those whose level of PA decreased experienced significant declines in HRQoL. In contrast, HRQoL improved in patients who maintained moderate or high levels of PA and those who increased their PA. We focused on a specific PA—walking—since it is a very common leisure-time activity that can easily be done by older individuals and those with medical conditions such as COPD.

In our univariate analysis, patients who engaged in low levels of PA had more dyspnea, more comorbidities, more hospital admissions in the 2 previous years, lower FEV_1, and poorer HRQoL than those with high PA. This corresponds to the results of a cross-sectional study that established comorbidities such as diabetes, HRQoL, and home oxygen therapy as determinants of low PA [28], and also with another study in which patients who had been hospitalized during the previous year for an exacerbation of COPD reported lower levels of PA than those who had not been hospitalized for a COPD exacerbation [29].

In a population-based cohort study, Garcia-Aymerich et al. showed that patients with even relatively low levels of PA (walking or pedaling for two hours per week) had a 28% lower risk of hospitalization due to COPD than those with little or no physical activity [13]. All-cause and respiratory mortality were also lower. The investigators did not, however, observe a dose-related response between level of PA and either hospitalizations or respiratory mortality.

Although preventing respiratory-related mortality is of utmost importance, improving quality of life should not be overlooked. In our study, patients with COPD who maintained low levels of PA or who decreased their PA over the study period experienced declines in HRQoL, whereas those who increased their PA or maintained moderate or high levels of PA demonstrated improvements in HRQoL in the specific HRQoL questionnaires and these changes were both statistically and clinically significant (increase of more than 4 units in the SGRQ).

To the best of our knowledge, this is the first study to evaluate the impact of changes in leisure-time PA on HRQoL among patients with COPD who are not taking part in a respiratory rehabilitation program**.** Respiratory rehabilitation programs have proved beneficial in improving health and HRQoL among patients with COPD [30]. However, these programs offer multiple features in addition to physical training that likely contribute to the benefits. To date, it has not been established which aspects of respiratory rehabilitation programs have the greatest impact on health, mortality, and HRQoL.

It is likely that PA improves HRQoL among patients with COPD for the same multifactorial reasons that it benefits the general population. PA improves cardiac function and increases maximum oxygen uptake. It has positive effects on blood pressure, lipid profiles, and clotting mechanisms. It is also associated with healthier lifestyles. Among patients with COPD, regular PA improves peripheral muscle function [31]. It also reduces hospital admissions [13], which have been shown to impair HRQoL [32].

Among patients with COPD, HRQoL appears to evolve differently when evaluated with a generic questionnaire (SF-36) than when it is evaluated using a disease-specific questionnaire. At the beginning of our study, patients reporting low levels of PA had the lowest HRQoL as measured by PCSS scores. Other investigators have observed similar associations among patients with COPD [28]. It has also been observed in healthy adults aged 60-89 years [33], where individuals who engaged in PA of moderate intensity for more than one hour per week had better HRQoL in 5 areas of the SF-36, including the 4 physical areas. In our study, the evolution of PCSS scores over 5 years of follow-up showed declines in HRQoL at all levels of PA compared to both baseline and to the general population. However, the decline in HRQoL was greater for patients who maintained low levels of PA or who decreased the amount of time engaged in PA.

Among patients with COPD, we are unaware of any study examining the impact of changes in PA on HRQoL measured with a generic questionnaire. In a study conducted among 3,891 healthy individuals followed for 3 years, higher PA during leisure time was associated with an improvement of HRQoL, especially in the mental components of SF-36, although the strength of the association was limited and the magnitude of the change would be likely to have no clinical significance [34]. In our study, patients with higher levels of PA had MCSS scores similar to those in the general population. Among patients with low and moderate PA who decreased the amount time engaged in PA over the 5-year study period, MCSS scores declined from baseline, with an even more striking difference than compared with the general population. In our study, the loss of HRQoL embodied in the PCSS likely reflects the natural decline in HRQoL with the passing of time. This tends to be especially pronounced among populations with a chronic disease such as COPD which has

substantial respiratory and systemic consequences. This corresponds to the overall trend toward declining HRQoL over time measured with a generic instrument such as the SF-36. Such changes are more pronounced in older age groups, and in the physical domains [35].

The strengths of our study include the large size of the cohort (611 patients), the fact that patients were recruited from general outpatient clinics, the long follow-up (5 years), and the use of 3 different questionnaires—2 of which are designed specifically for patients with COPD. Another strength of our study is that the patients did not receive any special study-related treatments or interventions such as a rehabilitation program during the follow-up period. Instead, they continued to follow the controls and treatments prescribed by their health-care providers, none of whom received any direction regarding treatment from the study authors. In addition to comparing levels of PA with HRQoL, we tracked changes in HRQoL over time and compared these to changes in a general population. We conducted statistical adjustments in an effort to prevent confounding factor from biasing the results.

Limitations of the study must also be noted. Since confounding and reverse causation are possible in this study, no causality or directionality of the findings can be inferred. We used a questionnaire to establish the level of PA rather than a direct measure such as an accelerometer or pedometer. At the time this study was performed, the use of more objective measures of assessment of PA such as triaxial accelerometers was not common, but they will become the new standard for PA measurements even in studies with larger samples [36]. Valid, questionnaires that measure PA may be useful as a group estimate, but their lack of accuracy and large individual variability indicate that relying on them on an individual basis is not

recommended [37]. Self-reports by study subjects may overestimate or underestimate PA. However, the scale we used, apart from having been validated and used in other studies of patients with COPD [13, 25], established differences between the 3 levels of PA in the “Physical Functioning” domain of the SF-36, which would support the discriminatory capacity of this instrument.

We also focused on walking as a measure of physical activity, and did not include other activities such as time spent doing domestic chores. While it is possible that other types of PA may influence HRQoL, in our environment walking is the most common form of leisure time PA. Another limitation of our study is the small sample size in some of the categories of PA change during the follow-up period. Although we were able to detect statistical and clinically significant changes in some of these categories, due to the small sample size those results should be interpreted cautiously. As expected, patients who died during the follow-up period had poorer physical activity and HRQoL at baseline than those who survived. This biases the results, which are based on survival, since we were not able to examine the changes in physical activity and HRQoL among those who died. Some non-studied factors may also play a role in the interaction between physical activity and quality of life in COPD.

The patient population was almost entirely comprised of men (97%). Similar gender distributions have been observed in other studies performed in Spain [38]. However this gender distribution could be different as have been shown in a recent epidemiological study [39]. Generalizing our results to the female population could not be appropriate.

In conclusion, we found that patients with COPD who maintained a low level of PA or who engaged in less PA over time were more likely to experience a significant

impairment in HRQoL. Patients who increased their levels of PA or maintained them at a higher level, in a low intensity activity such as walking for at least 2 hours per week, improved or maintained their HRQoL levels regardless of the baseline level of PA. This suggests that patients with COPD could significantly improve their HRQoL with only a minor increment in their leisure-time PA and without any special supervision. In addition to including patients with COPD in respiratory rehabilitation programs, interventions that increase PA, such as daily walking, could yield important improvements in HRQoL among patients with COPD. Future studies should incorporate more objective measures of PA, such as data from multiaxial accelerometers and evaluation of exercise capacity, include larger sample sizes of different PA categories, and provide longer follow-up.

Acknowledgements

This study was partially supported by grants no. 97/0326 from the Fondo de Investigación Sanitaria and the Research Committee Hospital Galdakao-Usansolo.

References

1. Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA. Dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc* 2001;33(6 Suppl):S351-358.
2. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all cause mortality. A prospective study of healthy men and women. *JAMA* 1989;273:1093-1098.
3. Siscovick DS, Fried L, Mittelmark M, Rutan G, Bild D, O´Leary DH. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. *Am J Epidemiol* 1997;145:977-986.
4. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423-1434.
5. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002;347:716-725.
6. Celli BR, MacNee W, Agusti A, Anzueto, B. Berg, A.S. Buist, P.M.A. Calverley, N. Chavannes, T. Dillard, B. Fahy, A. Fein, J. Heffner, S. Lareau, P. Meek, F. Martinez, W. McNicholas, J. Muris, E. Austegard, R. Pauwels, S. Rennard, A. Rossi, N. Siafakas, B. Tiep, J. Vestbo, E. Wouters and R. ZuWallack. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.

7. Gross NJ. Extrapulmonary effects of COPD. *Curr Opin Pulm Med.* 2001;7:84-92.

8. Ferrer M, Alonso J, Morera J, Marrades RM, Khalaf A, Aguar MC, Plaza V, Prieto L, Antó JM. Chronic obstructive pulmonary disease stage and health related quality of life. *Ann Intern Med* 1997;127:1072-1079.

9. Fan SF, Curtis JR, Tu SP, McDonell MB, Fihn SD. Using quality of life to predict hospitalizations and mortality in patients with chronic obstructive pulmonary disease. *Chest* 2002; 122:429-436.

10. Osman LM, Godden DJ, Friend JAR, Legge JS, Douglas JG. Quality of life re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997;52:67-71.

11. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Félez M, Khalaf A, Marrades RM, Monsó E, Serra-Batlles J, Antó JM. Health related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:680-685.

12. Bize R, Johnson JA, Plotnikoff RC. Physical activity level and health related quality of life in the general adult population: a systematic review. *Prev Med* 2007; 45: 401-415.

13. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006;61:772-778.

14. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Am J Respir Crit Care Med 2007; 175:458-463.

15. Sanchis J. Normativa para la espirometría forzada: Grupo de trabajo de la SEPAR para la práctica de la espirometría clínica. *Arch Bronconeumol* 1989;25: 132-142.

16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function test, European Community for Steel and Coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993;16:5-40.

17. Ware JE, Snow KK, Kosinsky M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute; 1993.

18. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991:85(Suppl B):25-31.

19. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773-778.

20. Alonso J, Prieto L, Ferrer M, Vilagut G, Broquetas JM, Roca J, Batlle JS, Antó JM. Testing the measurement properties of the Spanish version of the SF-36 health survey among male patients with chronic obstructive pulmonary disease. *J Clin Epidemiol* 1998;51:1087-1094.

21. Ferrer M, Alonso J, Prieto L, Plaza V, Monsó E, Marrades R, Aguar MC, Khalaf A, Antó JM. Validity and reliability of the St George's Respiratory Questionnaire after adaptation to a different language and culture: the Spanish example. *Eur Respir J* 1996;9:1160-1166.

22. Güell R, Casan P, Sangenís M, Plaza V, Monsó E, Marrades R, Aguar MC, Khalaf A, Antó JM. Quality of life in patient with chronic respiratory disease: the Spanish version of the chronic respiratory questionnaire (CRQ). *Eur Respir J* 1998;11:55-60.

23. Alonso J, Regidor E, Barrio G, Prieto L, Rodriguez C, de la Fuente L. Population reference values of the Spanish version of the Health Questionnaire SF-36. *Med Clin (Barc)* 1998;111:410-416.

24. Esteban C, Quintana JM, Aburto M, Moraza J, Capelastegui A. A simple score for assessing stable chronic obstructive pulmonary disease. QJM 2006; 99: 751-759.

25. Schnohr P, Scharling H, Jensen JS. Changes in leisure time physical activity and risk of death: An observational study of 7000 men and women. *Am J Epidemiol* 2003;158:639-644.

26. Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes: comparison with still active athletes of the same ages. *Circulation* 1968; 38:1104 -1115.

27. Saltin B. Physiological effects of physical conditioning. In: Hansen AT, Schnohr P, Rose G, eds. Ischaemic heart disease: the strategy of postponement. Chicago, IL: Year Book Medical Publishers, 1977: 104-115.

28. Garcia-Aymerich J, Félez MA, Escarrabil J, Marrades RM, Morera J, Elosua R, Antó JM. Physical activity and its determinants in severe chronic obstructive pulmonary disease. *Med Sci Sport Exe* 2004;36:1667-1673.

29. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. *Chest* 2006;129:536-544.

30. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Ionescu AA, Thomas J, Tunbridge J. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362-368.

31. Casaburi R. Skeletal muscle dysfunction in chronic obstructive pulmonary disease (review). *Med Sci Sports Exerc* 2001;33(7 suppl):S662-670.

32. Miravitlles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, Verea H, Murio C, Ros F, Vidal R. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax* 2004;59:387-395.

33. Acree LS, Longfors J, Fjeldstad AS, Fjeldstad C, Schank B, Nickel KJ, Montgomery PS, Gardner AW. Physical activity is related to quality of life in older adults. *Health Qual Life Outcomes* 2006;4:37.

34. Tessier S, Vuillemin A, Bertrais S, Tessier S, Vuillemin A, Bertrais S, Boini S, Le Bihan E, Oppert JM, Hercberg S, Guillemin F, Briançon S. Association between leisure-time physical activity and health-related quality of life changes over time. *Prev Med* 2007;44:202-208.

35. Hopman WM, Berger C, Joseph L, Towheed T, VandenKerkhof E, Anastassiades T, Adachi JD, Ioannidis G, Brown JP, Hanley DA, Papadimitropoulos EA; CaMos Research Group. The natural progression of health-related quality of life: results of a five-year prospective study of SF-36 scores in a normative population. *Qual Life Res* 2006;15:527-536.

36. Hagströmer M, Oja P, Sjöström M. Physical activity and inactivity in an adult population assessed by accelerometry. Med Sci Sports Exerc 2007; 39: 1502-1508.

37. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. *Eur Respir J* 2006; 27:1040-1055.

38. Soler-Cataluña JJ, Martinez-Garcia MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005; 60: 925-931.

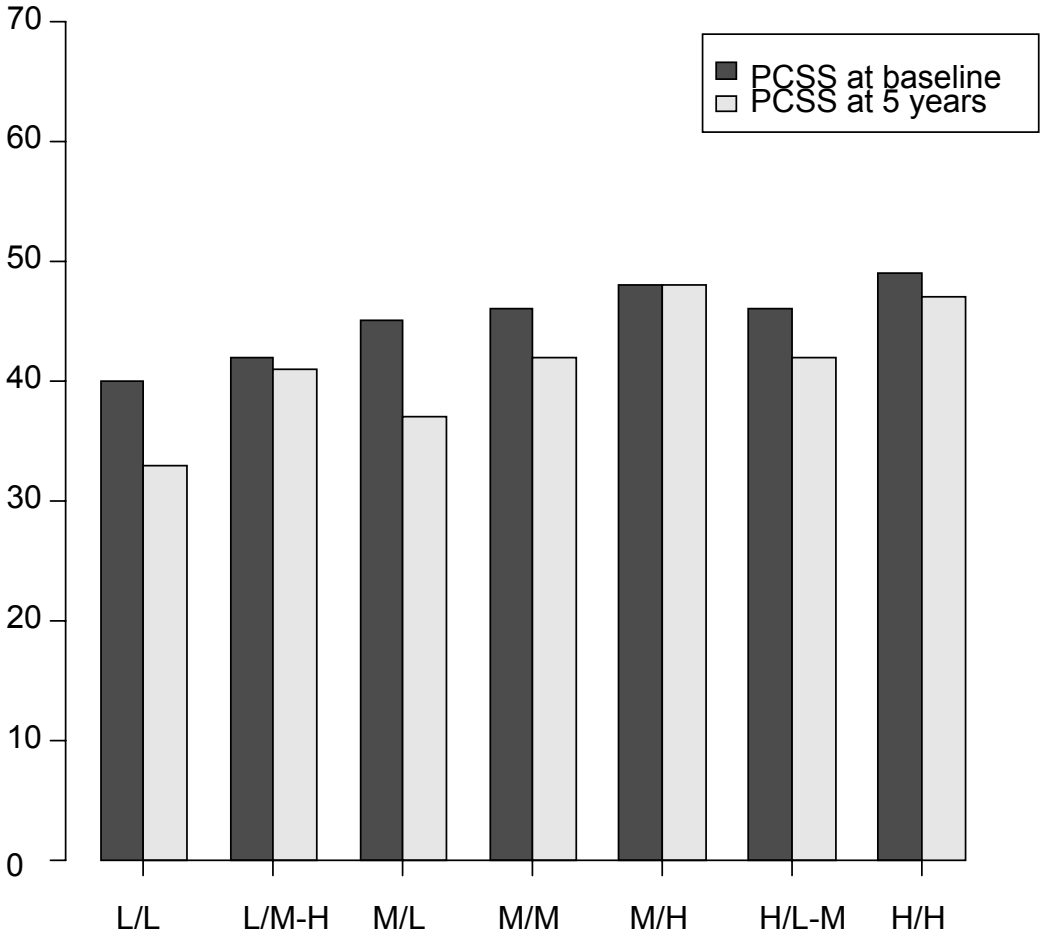
39. Miravitlles M, Soriano JB, García-Río F, Muñoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009; 64:863-868

Figure 1. Evolution of SF-36 summary scales in relation with changes in Physical Activity. Compared to normalized SF-36 values from the general population of similar age and gender.

Evolution of SF-36 summary scales scores from the beginning to 5 years for each category of physical activity.
50 points is the reference value of general population of similar age and gender as the patients' sample included.

Referred changes in physical activity from basal time to 5 years afterwards: L/L: from Low to Low physical activity; L/M-H: from Low to Moderate or High physical activity ; M/L: from Moderate to Low physical activity; M/M: from Moderate to Moderate physical activity; M/H: from Moderate to High physical activity; H/L-M: from High to Low or Moderate physical activity; H/H: from High to High physical activity.

Evolution of SF-36 physical component summary scale in relation with changes in Physical Activity



Evolution of SF-36 mental component summary scale (MCSS) in relation with changes in Physical Activity.

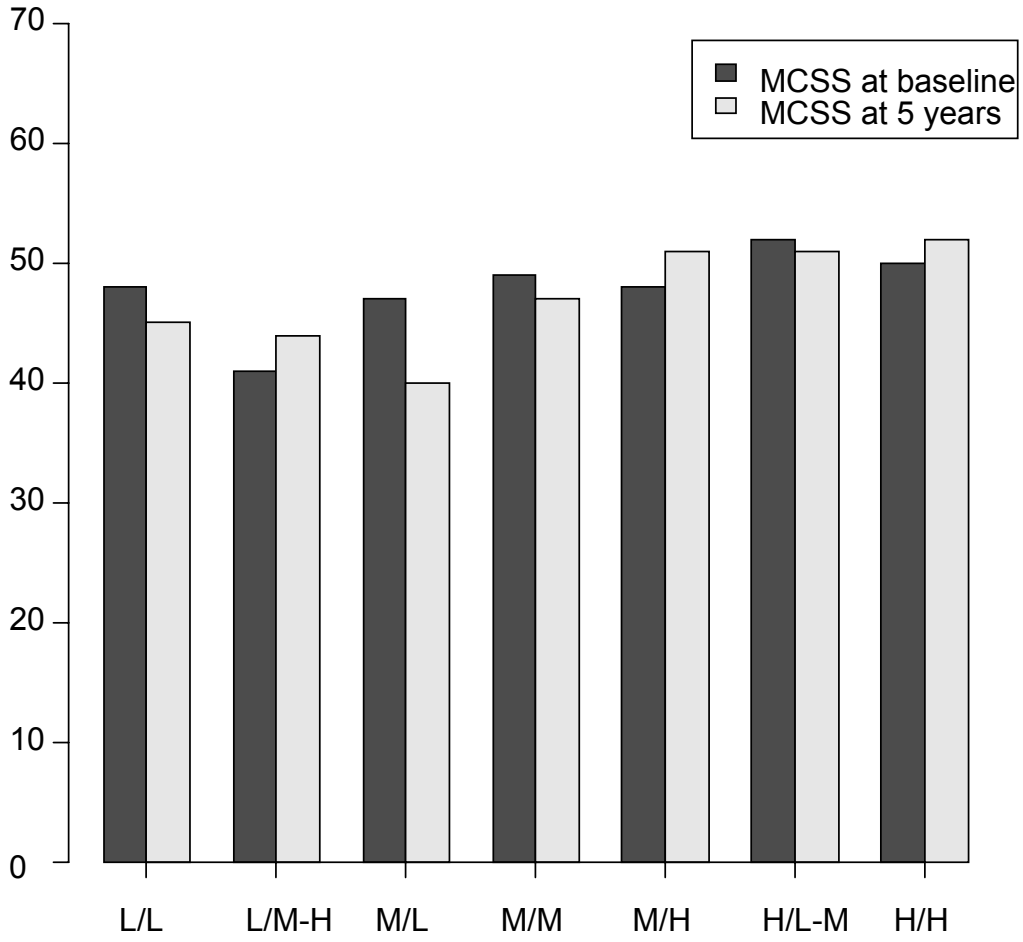

70
60
50
40
30
20
10
0
MCSS at baseline
MCSS at 5 years
L/L
L/M-H
M/L
M/M
M/H
H/L-M
H/H

Table 1. Baseline characteristics of study participants by survival status over a 5-year follow-up period.

	Survivors 445 (72.8%)	Non-survivors 166 (27.2%)	**P value**
Age (years)	65.5 (8.6)	70.1 (7.0)	<.0001
FEV_1 (L)	1.45 (0.46)	1.13 (0.38)	<.0001
$FEV_{1\%}$	52 (14)	43.6 (14)	<.0001
FEV_1/VC (%)	51.1 (10.2)	47.3 (10.1)	<.0001
BMI (kg/m^2)	27.9 (4.3)	27.5 (4.3)	0.28
Pack/years	44.9 (27.9)	55.6 (29.4)	<.0001
Current smokers	101 (22.7%)	29 (17.5%)	0.26
Dyspnea			<.0001
I	43 (9.7%)	1 (0.6%)	
II	243 (54.6%)	63 (37.9%)	
III	147 (33.0%)	86 (51.8%)	
IV-V	12 (2.7%)	16 (9.6%)	
COPD severity, n (%)			<.0001
GOLD staging II	249 (56%)	55 (33.1%)	
GOLD staging III	182 (40.9%)	85 (51.2%)	
GOLD staging IV-V	14 (3.15%)	26 (15.7%)	
Level of Physical Activity			<.0001
Low	50 (11.2%)	45 (27.1%)	
Moderate	231 (51.9%)	98 (59.0%)	
High	164 (36.8%)	23 (13.9%)	
St. George Respiratory Questionnaire (SGRQ)			
Activity	50.4 (21.1)	62.0 (18.6)	<.0001
Impact	30.4 (19.5)	38.9 (17.5)	<.0001
Symptoms	40.5 (20.9)	47.0 (20.7)	0.0005
Total SGRQ	38.2 (18.2)	47.3 (16.1)	<.0001
Hospitalizations in the 2 years prior to baseline, n (%)			<.0001
0	309 (69.4%)	78 (47%)	

1-2	115 (25.8%)	62 (37.3%)	
≥3	21 (4.7%)	26 (15.6%)	
Comorbidities, n (SD)	1.6 (1.25)	1.5 (1.20)	0.37

Data are presented as mean (SD) or number (%).
BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; $FEV_{1\%}$: FEV_1 as a percentage of the predicted value; GOLD: Stages of the disease by Global Initiative for Chronic Obstructive Lung Disease; SGRQ: Saint George's Respiratory Questionnaire; VC: vital capacity.

Table 2: Baseline characteristics of the 391 survivors who completed the three HRQoL instruments after 5 years of follow-up.

Level of Physical Activity	Low [a] (41)	Moderate [b] (207)	High [c] (143)	p-value
Age	65.8 ± 8.6 [c]	67.3 ± 7.1 [c]	61.9 ± 9.7 [ab]	<.0001
FEV_1 (L)	1.36 ± 0.50	1.43 ± 0.44[c]	1.56 ± 0.48 [b]	0.01
$FEV_{1\%}$	51.4 ± 16.3 [bc]	51.9 ± 13.6 [ac]	53.3 ± 13.7 [ab]	<.0001
BMI	28.2 ± 6.7	27.9 ± 3.9	28.0 ± 4.1	0.94
Pack-year smoking habit	46.4 ± 28.2	43.7 ± 30.2	44.0 ± 25.1	0.85
Comorbidities	2.2 ± 1.4 [bc]	1.7 ± 1.2 [a]	1.5 ± 1.2 [a]	0.003
Dyspnea				<.0001
I	0	7 (3.4)	32 (22.4)	
II	11 (26.8)	117 (56.5)	85 (59.4)	
III	26 (63.4)	80 (38.6)	25 (17.5)	
IV-V	4 (9.8)	3 (1.5)	1 (0.7)	
GOLD staging				0.90
I	21 (51.2)	117 (56.5)	85 (59.4)	
II	19 (46.3)	84 (40.6)	54 (37.8)	
III-IV	1 (2.4)	6 (2.9)	4 (2.8)	
Smoking status				0.30
Current smoker	7 (17.7)	39 (18.8)	39 (27.3)	
Ex-smoker	31 (75.6)	158 (76.3)	99 (69.2)	
Never smoker	3 (7.3)	10 (4.8)	5 (3.5)	
Hospitalizations for COPD exacerbation in the 2 years prior to enrollment				0.001
0	22 (53.6)	136 (65.7)	117 (81.8)	
1	11 (26.8)	46 (22.2)	19 (13.3)	
≥ 2	8 (19.5)	25 (12.1)	7 (4.9)	

Chi-square tests for the comparison of proportions among the three physical activity categories. BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; $FEV_{1\%}$: FEV_1 as a percentage of the predicted value; GOLD: Stages of the disease by Global Initiative for Chronic Obstructive Lung Disease

Superscript letters indicated differences among the three physical activity categories by Scheffé test for multiple comparisons for continuous variables at $p<0.05$.

Table 3. Baseline HRQoL across PA categories as measured by two disease-specific and one generic instrument.

Physical Activity	Low [a] (n=41)	Moderate [b] (n=207)	High [c] (n=143)	p-value
St. George Respiratory Questionnaire (SGRQ)				
Activity	64.1 ± 18.9 [bc]	52.2 ± 20.7 [ac]	43.5 ± 20.5 [ab]	<.0001
Impact	40.3 ± 21.1 [bc]	31.2 ± 19.0 [ac]	25.9 ± 17.6 [ab]	<.0001
Symptoms	45.5 ± 25.7 [c]	42.4 ± 20.0 [c]	35.8 ± 20.4 [ab]	0.004
Total SGRQ	48.4 ± 19.3 [bc]	39.4 ± 17.7 [ac]	32.9 ± 16.8 [ab]	<.0001
Chronic Respiratory Questionnaire (CRQ)				
Mastery	18.8 ± 6.8 [c]	20.2 ± 5.6 [c]	21.9 ± 5.6 [ab]	0.002
Dyspnea	22.1 ± 9.0 [c]	25.2 ± 8.2	26.4 ± 7.9 [a]	0.01
Fatigue	15.9 ± 5.8 [bc]	18.7 ± 5.5 [a]	19.5 ± 5.4 [a]	0.001
Emotional function	33.6 ± 10.8	35.5 ± 9.9	36.9 ± 8.7	0.1
Total CRQ	90.3 ± 27.8 [c]	99.5 ± 25.0	104.8 ± 23.3 [a]	0.003
Medical Outcomes Study Short Form (SF-36)				
Physical component summary score (PCSS)	40.6 ± 8.1 [bc]	45.7 ± 7.4 [a]	47.3 ± 7.8 [a]	<.0001
Mental component summary score (MCSS)	46.5 ± 15.1 [c]	49.6 ± 11.0	51.4 ± 9.3 [a]	0.03
Physical Functioning	44.7 ± 23.4 [bc]	64.0 ± 20.2 [ac]	72.7 ± 18.9 [ab]	<.0001
Role Physical	62.2 ± 41.9 [bc]	80.5 ± 33.8 [a]	81.8 ± 33.1 [a]	0.004
Bodily Pain	62.1 ± 31.7	71.8 ± 27.4	73.4 ± 25.4	0.06
General Health	42.0 ± 24.9 [c]	47.0 ± 21.4	51.6 ± 22.0 [a]	0.02
Vitality	51.6 ± 24.9 [bc]	62.0 ± 22.4 [a]	67.8 ± 23.7 [a]	0.0003
Social Functioning	76.8 ± 26.4 [c]	83.4 ± 21.4	87.3 ± 20.3 [a]	0.01
Role Emotional	65.0 ± 44.7 [bc]	83.1 ± 34.9 [a]	87.6 ± 30.0 [a]	0.001
Mental Health	70.7 ± 26.6 [c]	75.9 ± 21.9	80.1 ± 18.7 [a]	0.02

Data are presented as mean (SD)
Superscript letters indicated differences among the three physical activity categories by Scheffé test for multiple comparisons for continuous variables at $p<0.05$.

Table 4. Relationship of changes in physical activity and HRQoL status at 5 year and changes from baseline.

Baseline Level of Physical Activity	Physical Activity after 5 Years of Follow-up (N)	Total SGRQ Score at 5 years	Total SGRQ difference vs baseline	Total CRQ score at 5 years	Total CRQ difference vs baseline	SF-36-PCSS at 5 years	SF-36-PCSS difference vs baseline	SF-36-MCSS at 5 years	SF-36-MCSS difference vs baseline
Low	Low (15) [a]	57.8 (22.6)	-10.6 (17.5) [be]	81.7 (31.8)	-11.5 (19.8) [e]	31.1 (5.2)	-8.2 (5.1) [eg]	48.3 (12.4)	-2.4 (8.6)
Low	Moderate/High (26) [b]	40.9 (23.0)	8.1 (17.1) [ac]	89.3 (31.4)	0.6 (13.9)	37.8 (7.6)	-3.5 (8.7)	47.3 (14.8)	3.2 (14.0)
Moderate	Low (19) [c]	59.0 (17.0)	-12.4 (10.0) [be]	81.9 (25.4)	-11.4 (10.7) [eg]	33.7 (7.3)	-10.2 (5.3) [eg]	44.8 (13.7)	-3.8 (12.2)
Moderate	Moderate (152) [d]	40.9 (19.2)	-1.8 (16.2)	99.5 (26.6)	-0.8 (16.3)	39 (8.9)	-6.4 (8.7) [g]	50.4 (11.7)	0.5 (10.8)
Moderate	High (36) [e]	29.4 (20.3)	7.8 (14.8) [acf]	106.3 (30.5)	6.6 (16.6) [ac]	44.3 (7.7)	-3.1 (8.7) [ca]	52.4 (11.2)	3.2 (9.5)
High	Moderate/Low (56) [f]	41.8 (21.2)	-4.9 (20.0) [e]	102.1 (24.7)	0.5 (16.9)	38.8 (9.6)	-7.0 (9.8) [g]	52.9 (10.4)	0.2 (11.4)
High	High (87) [g]	28.2 (15.9)	2.1 (14.4)	110.5 (22.7)	3.7 (16.4) [c]	44 (7.4)	-4.3 (8.1) [dfca]	53.2 (9.9)	2.5 (13.4)

Data are presented as mean (SD). Positive values indicate an improvement in HRQoL, negative values a decline in HRQoL. SGRQ score improvements has been changed to positive values and impairment has been changed to negative values. Superscript letters indicated differences among the three physical activity categories by Scheffé test for multiple comparisons at $p<0.05$ for continuous variables. SGRQ: Saint George's Respiratory Questionnaire; CRQ: Chronic Respiratory Questionnaire; PCSS: SF-36 Physical Component Summary Scale; MCSS: SF-36 Mental Component Summary Scale.

Table 5. Multivariate analysis of physical activity changes and HRQoL changes from basal time to 5 year follow-up adjusted by relevant variables.

Level of PA	Model 1: Total SGRQ score		Model 2: Total CRQ score	
Baseline/5 years	β estimate	p value	β estimate	p value
Low/Low	Reference		Reference	
Low/Moderate-High	15.9	0.0005	8.7	0.05
Moderate/Low	-0.7	0.87	2.6	0.56
Moderate/Moderate	10.2	0.007	10.3	0.005
Moderate/High	18.4	<.0001	14.8	0.0004
High/Moderate-Low	8	0.05	10.7	0.005
High/High	16.9	<.0001	13.6	0.0003

Positive values indicate an improvement in HRQoL, negative values a decline in HRQoL. SGRQ score improvements has been changed to positive values and impairment has been changed to negative values.

Multivariate models where the dependent variables were the change in the total SGRQ score (Model 1) and the total CRQ score (Model 2) from baseline to 5 years. The main independent variable in Model 1 was the change in physical activity over the 5-year period, adjusted by age, dyspnea, $FEV_{1\%}$, hospital admissions for COPD exacerbations in the 2 years prior to enrollment, comorbidities, and mental health status (measured by the SF-36 MCS1) all at baseline, as well as by baseline HRQoL measured by the total SGRQ score. The main independent variable in Model 2 was the change in physical activity over the 5-year study period adjusted by hospital admissions for COPD exacerbations in the 2 years prior to enrollment and baseline mental health status (measured by the SF-36 MCS1) as well as by the baseline HRQoL levels at the beginning of the study measured by the total CRQ score. Reference group for comparison in both models: those who had low level of physical activity at the beginning and also at 5 years of follow-up.