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ORIGINAL ARTICLE

Influence of changes in physical activity on frequency of hospitalization in chronic obstructive pulmonary disease

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ABSTRACT

Background and objective: **To evaluate whether changes in regular physical activity (PA) in patients with chronic obstructive pulmonary disease (COPD) affect the rate of hospitalizations for COPD exacerbation (eCOPD).**
Methods: **Five hundred forty-three ambulatory clinic patients being treated for COPD were prospectively identified. PA was self-reported by patients, and the level was established by the distance they walked (km/day) at least 3 days per week. Hospitalizations were recorded from hospital databases. All patients with at least a 2-year follow-up after enrolment were included in the analysis. The response variable was the number of hospitalizations for eCOPD within the 3-year period from 2 to 5 years after study enrolment.**
Results: **Three hundred ninety-one survivors were studied. Mean forced expiratory volume in 1 s was 52% (±14%) of the predicted value. Patients who maintained a lower level of PA had an increased rate of hospitalization (odds ratio 1.901; 95% confidence interval 1.090–3.317). After having had the highest level of PA, those patients who decreased their PA in the follow-up showed an increasing rate of hospitalizations (odds ratio 2.134; 95% confidence interval 1.146–3.977).**
Conclusions: **Patients with COPD with a low level of PA or who reduced their PA over time were more likely to experience a significant increase in the rate of hospitalization for eCOPD. Changes to a higher level of PA or maintaining a moderate or high level of PA over time, with a low intensity activity such as walking for at least 3–6 km/day, could reduce the rate of hospitalizations for eCOPD.**

Key words: chronic obstructive pulmonary disease, hospitalization, physical activity.

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SUMMARY AT A GLANCE

This study investigated if a change in physical activity had any influence on hospitalizations for COPD exacerbation. We found an association between the change in physical activity and hospitalizations, patients who increased or maintained a moderate level of physical activity had fewer hospitalizations for COPD exacerbation.

Abbreviations: COPD, chronic obstructive pulmonary disease; eCOPD, COPD exacerbation; FEV_1, forced expiratory volume in 1 s; PA, physical activity.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by periodic exacerbations (eCOPD). The number of yearly exacerbations is closely associated with the severity of the disease,[1,2] but they are experienced by patients in all severity categories.[3] Exacerbation and its most severe form, hospitalization, exert a substantial impact on COPD, having been associated with decreased lung function,[4] increased cost of COPD treatment,[5,6] increased risk of mortality,[7] and short-term[8] and long-term[9,10] effects on health-related quality of life.

In the general population, regular physical activity (PA) has been shown to be beneficial for the primary and secondary prevention of cardiovascular disease and several other conditions like diabetes or hypertension,[11] as well as being associated with reduced mortality.[12] In addition, PA has been associated with a decrease in the use of health resources.[13,14] Walking, an activity that most people can do, has been associated with all the benefits of regular PA.[15]

COPD patients are less likely to engage in regular PA than healthy individuals.[16] However, regular PA has been associated with reduced risk of hospitalization for eCOPD and mortality among patients with COPD.[17] Indeed, even a low level of PA such as walking a minimum of 2 h/week has been associated with decreased risk of hospitalization for eCOPD.[18]

Guidelines for the diagnosis and management of COPD are beginning to recognize the importance of PA for COPD patients.[19] However, there are a limited number of studies evaluating the relationship between PA and eCOPD hospitalizations.

We designed this study to determine the impact of changes in walking during leisure time, a low-intensity PA, on frequency of hospitalizations for eCOPD over a 5-year period.

METHODS

Subjects

We recruited patients being treated for COPD at five outpatient respiratory clinics affiliated with the Hospital Galdakao-Usansolo between January 2003 and January 2004.

Patients were consecutively included in the study if they had been diagnosed with COPD for at least 6 months and had been receiving medical care at one of the hospital respiratory outpatient facilities for at least 6 months. Their COPD had to be stable for 6 weeks before enrolment. Other inclusion criteria were forced expiratory volume in 1 s (FEV_1) <80% of the predicted value and a FEV_1/forced vital capacity quotient <70%. 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 the year before the beginning of the study. Each patient was given detailed information about the study and had to provide informed consent to take part in it. The study protocol was approved by the research committee of the Hospital Galdakao-Usansolo (03/09062005).

Study protocol

Spirometry was conducted following criteria from the Spanish Pneumology and Thoracic Surgery Society[20] with a Master-Lab Body (Erich Jaeger GmbH, Würzburg, Germany). Theoretical values were those established by the European Community for Steel and Coal.[21]

At the baseline personal interview, patients were asked about the kinds of PA they had engaged in during the previous year. Special emphasis was placed on walking (they had to leave home specifically for walking at least 3 days/week). Those patients who walked 2 or less days per week were classified as 'non-regular PA doers'. The regular walkers were classified based on the distance they covered each day into five categories: non-regular PA (nr-PA); walking as a specific activity: no more than 3 km/day (low PA); between 3 and 6 km/day (moderate PA); more than 6 km/day (high PA); and sport or non-sedentary works (very high PA). Change in PA during the study was determined by comparing PA at enrolment and 2 years after enrolment. Taking into account the number of individuals in each cell, there were 25 possible combinations. Seven categories of change in PA were considered from the five levels of PA reported by patients at the two points in time (Table 1).

Level of dyspnoea was established using a scale adapted from Fletcher *et al.*[22]

Health-related quality of life was assessed using the generic Short Form 36 Health Survey (SF-36)[23] and the

Table 1 Observed frequencies (number of subjects in each cell) obtained from the cross-tabulation between both measurements of physical activity, at baseline and 2 years after enrolment

	Physical activity 2 years after enrolment				
Physical activity at baseline	nr-PA (*n* = 86)	Low: ≤3 km/day (*n* = 131)	Moderate: >3 and ≤6 km/day (*n* = 126)	High: >6 km/day (*n* = 55)	Working/sports (*n* = 30)
nr-PA (*n* = 90)	54	28	8	0	0
Low: ≤3 km/week (*n* = 109)	17	69	20	2	1
Moderate: >3 and ≤6 km/week (*n* = 108)	11	23	62	12	0
High: >6 km/week (*n* = 75)	2	3	29	39	2
	2	8	7	2	27

Change in physical activity has been defined in seven categories based on these frequencies, and it has been indicated by different shade in grey in the table.

Each category of change in physical activity is codified by an integer number, from 1 to 7, and it is represented by a different shade of grey:

1 = From nr-PA (non-regular walkers) to nr-PA/low (*n* = 82).
2 = From low to nr-PA or from moderate to nr-PA/low (*n* = 51).
3 = From low to low (*n* = 69).
4 = From nr-PA/low to moderate/high/working/sports or from moderate to high/working/sports (*n* = 43).
5 = From moderate to moderate (*n* = 62).
6 = From high/working/sports to nr-PA/low/moderate (*n* = 51).
7 = From high/working/sports to high/working/sports (*n* = 70).

nr-PA, non-regular physical activity; PA, physical activity.

Saint George's Respiratory Questionnaire that is specific for respiratory-related health-related quality of life.[24] The SF-36 includes eight categories and two summary scales. Each category receives a score between 0 and 100 (with 100 representing the best health condition). The Saint George's Respiratory Questionnaire includes three categories: symptoms, impact and activity, as well as a global score. Each area receives a score between 0 and 100, with 0 representing a complete lack of deterioration. We used versions that have been validated in Spanish populations.[25,26]

Comorbidities were determined by reviewing patients' medical records. From them, we calculated the Charlson Comorbidity Index.[27] Six-minute walking tests were performed according to American Thoracic Society guidelines.[28]

Follow-up

Patients were followed for up to 5 years. Figure 1 shows the measurements at different time points of the study. No interventions were performed related to this study, and the research team did not take part in patients' routine treatment or the treatment of exacerbations. No patients took part in a rehabilitation program during the follow-up period.

Every year during the 5-year follow-up, survivors were interviewed and underwent the previously described measurements. As baseline, each patient was asked about the average distance they walked per day. Follow-up interviews were scheduled when patients were clinically stable. Patients who developed cancer, Alzheimer's disease or other condition that could interfere with the results were withdrawn from the study, along with those who could not be interviewed personally during the follow-up period.

All information of the follow-up was retrieved from the hospital database medical records. All reported deaths and dates of deaths were confirmed by reviewing medical reports, examining the hospital database and public death registries.

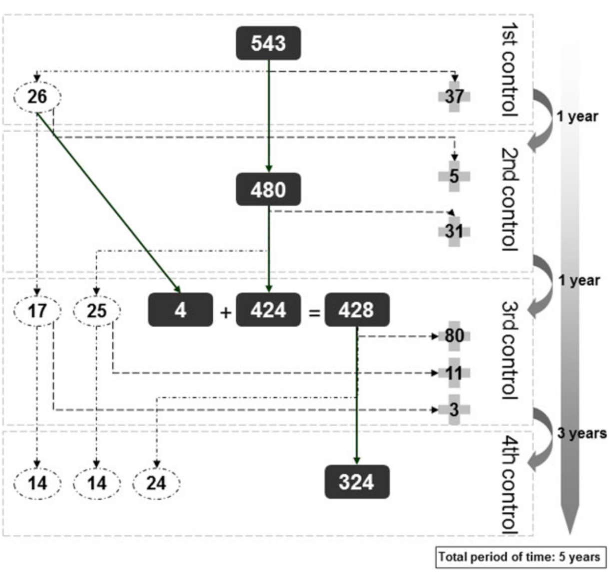

Figure 1 Follow-up cohort flowchart. (◌) withdrawn; (✚) deceased; (▬) followed.

Statistical analysis

Univariate comparison of continuous variables by level of categorical variables was performed using analysis of variance for normally distributed variables and the Wilcoxon and Kruskal–Wallis tests for non-normally distributed variables, depending on the number of categories. Univariate analysis for categorical variables was performed with chi-square or the Fisher's exact test.

All patients with a 2-year follow-up after enrolment were included in the analysis. Univariate Poisson regression was used to check the influence of several covariates on the rate of COPD-related hospitalizations during a 3-year period. The response variable was the number of hospitalizations for eCOPD in the period from 2 to 5 years after enrolment in the study. The time period for recoding the number of hospitalizations was calculated as the period between the visits at the second and fifth year after the enrolment for patients with complete follow-up, and as the period between the visits at 2 years after enrolment and the date of death or date of withdrawal for deceased and withdrawn patients, respectively.

The following variables were considered as covariates of interest: age; gender; FEV_1% predicted; smoking habit; dyspnoea; Charlson comorbidity index; previous hospitalizations for eCOPD in the 2 years prior to enrolment; hospitalizations for eCOPD in the first 2 years after enrolment, the 6-min walking test; and change in PA from baseline to 2 years after enrolment. All covariates that were statistically significant at the univariate level were included in a multivariate Poisson regression model with the same response variable. The final multivariate model included only those covariates with a statistically significant influence on the rate of hospitalization for COPD in the period from 2 to 5 years after enrolment in the study. Results for the final model were expressed in terms of odds ratios and their 95% confidence intervals, which were calculated by taking the exponential of the coefficients of the Poisson regression model and their 95% confidence interval.

Statistical significance was stated at $\alpha = 0.05$ level. All statistical analyses were performed using SAS System, v. 9.2 (SAS institute, Inc, Carey, NC, USA).

RESULTS

The general characteristics of this cohort of 543 patients are described in Table 2. Those in the highest level of PA were younger, had less dyspnoea, less airflow obstruction, higher walked distance in the 6-min walking test, fewer comorbidities, better health-related quality of life and fewer eCOPD admissions during the 2 years previous to enrolment.

Changes in PA from baseline to 2 years after enrolment, and the distribution of patients in the PA categories, are shown in Table 1. The majority of patients maintained the same level of PA over this period.

Table 2 General characteristics of the cohort at baseline by level of physical activity

	Total	Physical activity at baseline					
	(*n* = 543)	nr-PA (*n* = 125)	Low: ≤3 km/day (*n* = 155)	Moderate: >3–≤6 km/day (*n* = 131)	High: >6 km/day (*n* = 83)	Working/sports (*n* = 49)	*P*†
Gender (male)	522 (96.1)	118 (94.4)	149 (96.1)	125 (95.4)	83 (100.0)	47 (95.9)	NS
Age (years)	**68.3 (8.3)**	**69.8 (7.7)**	**71.2 (7.0)**	**69.2 (6.8)**	**67.3 (6.5)**	**54.8 (7.1)**	**<0.001**
BMI (kg/m^2)	28.3 (4.4)	27.4 (4.3)	28.3 (4.7)	28.6 (4.2)	28.4 (3.7)	29.1 (5.1)	NS
Dyspnoea							<0.001
1	69 (12.7)	8 (6.4)	10 (6.5)	23 (17.6)	20 (24.1)	8 (16.3)	
2	264 (48.6)	53 (42.4)	62 (40.0)	66 (50.4)	52 (62.7)	31 (63.3)	
3	166 (30.6)	42 (33.6)	67 (43.2)	38 (29.0)	10 (12.1)	9 (18.4)	
4–5	44 (8.1)	22 (17.6)	16 (10.3)	4 (3.1)	1 (1.2)	1 (2.0)	
FEV_1 (mL)	1464 (441.3)	1383 (473)	1355 (412)	1416 (378)	1633 (322)	1863 (490)	<0.001
FEV_1% predicted	**55.0 (13.3)**	**52.1 (13.9)**	**53.5 (14.3)**	**55.0 (12.1)**	**60.9 (10.1)**	**57.1 (13.4)**	**<0.001**
FEV_1/VC (%)		53.2 (9.6)	53.2 (9.2)	55.0 (9.4)	57.7 (8.4)	55.3 (9.2)	0.003
FEV_1GOLD							<0.001
<30%	18 (3.3)	9 (7.2)	5 (3.2)	3 (2.3)	0 (0.0)	1 (2.0)	
30–49%	167 (30.8)	44 (35.2)	57 (36.8)	44 (33.6)	9 (10.8)	13 (26.5)	
50–80%	358 (65.9)	72 (57.6)	93 (60.0)	84 (64.1)	74 (89.2)	35 (71.4)	
Smoking status							NS
Current smoker	114 (21.0)	32 (25.6)	22 (14.2)	25 (19.1)	12 (14.5)	23 (46.9)	
Former smoker	414 (76.2)	91 (72.8)	128 (82.6)	100 (76.3)	69 (83.1)	26 (53.1)	
No smoker	15 (2.8)	2 (1.6)	5 (3.2)	6 (4.6)	2 (12.4)	0 (0.0)	
Packs/year: $\bar{x}$ (SD)	46.8 (27.3)	49.2 (26.5)	50.0 (31.9)	44.4 (24.6)	41.9 (24.0)	46.0 (25.0)	<0.001
6-min walking test: (m) $\bar{x}$ (SD) (m)	**408.9 (92.4)**	**362.4 (98.0)**	**378.0 (79.5)**	**417.3 (77.3)**	**475.8 (64.9)**	**489.2 (69.0)**	**<0.001**
Hospitalizations for COPD exacerbations in the 2 years prior to enrolment:							**<0.001**
0	**402 (74.0)**	**85 (68.0)**	**92 (59.4)**	**108 (82.4)**	**74 (89.2)**	**43 (87.8)**	
1	**87 (16.0)**	**22 (17.6)**	**40 (25.8)**	**13 (9.9)**	**6 (7.2)**	**6 (12.2)**	
≥2	**54 (10.0)**	**18 (14.4)**	**23 (14.8)**	**10 (7.6)**	**3 (3.6)**	**0 (0.0)**	
Charlson Index	**2.4 (1.4)**	**2.5 (1.4)**	**2.7 (1.6)**	**2.4 (1.3)**	**2.0 (1.2)**	**1.9 (1.2)**	**<0.001**
SGRQ total	**39.2 (20.1)**	**44.7 (19.6)**	**44.3 (19.9)**	**36.3 (19.3)**	**29.4 (17.8)**	**33.2 (19.0)**	**<0.001**
SGRQ activity	**48.7 (24.9)**	**57.4 (23.8)**	**56.8 (23.3)**	**44.6 (23.3)**	**32.2 (22.6)**	**39.7 (21.5)**	**<0.001**
SF-36: physical activity	**57.8 (24.4)**	**47.9 (26.2)**	**50.1 (21.8)**	**62.1 (22.2)**	**73.8 (18.4)**	**68.4 (21.0)**	**<0.001**

† Kruskall–Wallis or analysis of variance for continuous variables and chi-square test for categorical variables except for FEV_1 GOLD, where Fisher's exact test was used due to small frequencies.

BMI (body mass index), bodyweight in kilograms divided by square of height; Dyspnoea, scale adapted from Fletcher *et al.*[22]; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; nr-PA, non-regular physical activity; PA, physical activity; Packs/year, number of cigarettes smoked per day × number of years smoked/20; SD, standard deviation; SF-36, Short Form 36 Health Survey; SGRQ, Saint George's Respiratory Questionnaire; VC, vital capacity.

Univariate analysis of the influence of changes in PA on the hospitalization rate showed that increasing or maintaining a higher level of PA diminished the odds of being hospitalized for eCOPD, while decreasing PA or maintaining a low level of PA was associated with a statistically significant increase in the hospitalization rate (Table 3).

Multivariate analysis showed that change in PA was independently associated with the hospitalization

Table 3 Univariate Poisson regression with frequency of hospitalizations for eCOPD from 2 to 5 years after study enrolment as the response variable and variables that could influence in the rate of hospitalizations

Covariate	Beta	SD	*P*	Exp(Beta) = OR	95% CI
Change in PA‡					
1	**1.197**	**0.324**	**0.0002**	**3.310**	**(1.753–6.248)**
2	**1.488**	**0.347**	**<0.0001**	**4.429**	**(2.246–8.735)**
3	**1.245**	**0.338**	**0.0002**	**3.471**	**(1.790–6.733)**
4	**0.915**	**0.372**	**0.014**	**2.496**	**(1.203–5.176)**
5	**0.218**	**0.380**	**0.566**	**1.214**	**(0.591–2.620)**
6	**0.771**	**0.375**	**0.040**	**2.162**	**(1.035–4.510)**
7†	—	—	—	—	
Age (continuous)	0.042	0.011	<0.0001	1.043	(1.021–1.065)
Hospitalizations for COPD exacerbations in the 2 years prior to enrolment					
0†	—	—	—	—	—
1	**1.004**	**0.202**	**<0.0001**	**2.729**	**(1.840–4.051)**
>1	**1.420**	**0.188**	**<0.0001**	**4.063**	**(2.863–5.972)**
Hospitalizations for COPD exacerbations in the first 2 years after enrolment					
0†	—	—	—	—	—
1	**1.036**	**0.242**	**<0.0001**	**2.818**	**(1.745–4.522)**
>1	**1.557**	**0.211**	**<0.0001**	**4.742**	**(3.138–7.168)**
Hospitalizations for COPD exacerbations in the whole 4 year period§					
0†	—	—	—	—	—
1	**1.029**	**0.215**	**<0.0001**	**2.798**	**(1.837–4.267)**
>1	**1.786**	**0.171**	**<0.0001**	**5.966**	**(4.267–8.331)**
FEV_1% (continuous)	–0.032	0.007	<0.0001	0.968	(0.956–0.982)
FEV_1 GOLD					
>30%	0.751	0.421	0.074	2.119	(0.929–4.840)
30–49	0.653	0.178	0.0002	1.921	(1.355–2.724)
50–80†	—	—	—	—	—
Dyspnoea					
1	–1.539	0.387	<0.0001	0.215	(0.101–0.458)
2	–0.956	0.308	0.002	0.385	(0.210–0.703)
3	–0.583	0.310	0.059	0.558	(0.304–0.978)
4–5	—	—	—	—	—
6-min walking test (m)	–0.005	0.001	<0.0001	0.996	(0.994–0.997)

All patients with follow-up at 2 years after enrolment where included in the sample (n = 428). The time period to estimate the number of hospitalizations was calculated as the period between the two visits for patients with complete follow-up (324 patients) and as the period between the visits at 2 years after enrolment and the date of death or the date of withdrawal for deceased and excluded patients (24 and 80 patients, respectively). Dyspnoea, scale adapted from Fletcher *et al.*[22]

† Reference category. Influence of smoking habit (as current smoker/former smoker/non-smoker and number of packs per year), gender and Charlson index (as 0–1/2–3/>3 and continuous) were not included in the table because they were not statistically significant.

‡ Coding for change in physical activity is the following:

1 = nr-PA to nr-PA/low.

2 = Low to nr-PA or moderate to nr-PA/low.

3 = Low to low.

4 = nr-PA/low to moderate/high or moderate to high.

5 = Moderate to moderate.

6 = High to nr-PA/low/moderate.

7 = High to high (reference).

§ It includes the 2 years prior to enrolment plus the first 2 years after enrolment.

—, 95% CI; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eCOPD, COPD exacerbation; FEV_1, forced expiratory volume in 1 s; GOLD, stages of the disease by Global Initiative for Chronic Obstructive Lung Disease; nr-PA, non-regular physical activity; OR, odds ratio; PA, physical activity; SD, standard deviation.

rate for eCOPD after adjustment by variables such as age, FEV_1% predicted and prior hospitalizations for eCOPD (Table 4).

Patients 'nr-PA' or 'low PA' had approximately double the expected rate of eCOPD-related hospitalizations compared with those who maintained the highest level of PA (odds ratio 1.901; 95% confidence interval 1.090–3.317). Among patients with the highest level of PA at baseline (walking >6 km/day, engaging in sports or working in a non-sedentary workplace), those who decreased their regular PA during the follow-up period were expected to have a higher rate of eCOPD-related hospitalizations (odds ratio 2.134; 95% confidence interval 1.146–3.977). Among patients who increased their level of regular PA from lower or moderate level to moderate or higher level, we observed no statistically significant difference in the rate of eCOPD-hospitalizations compared with more active patients (odds ratio 1.509; 95% confidence interval 0.817–2.786) (Table 5).

DISCUSSION

No previous studies have focused on change in PA in COPD patients. In this study, we demonstrate that among patients with COPD, changes in the level of PA (primarily walking) over 2 years of follow-up were associated with the rate of hospitalizations for eCOPD in the next 3 years of follow-up. Patients with no regular PA or those who maintained a lower level of PA or those who decreased their level of PA had significantly higher odds of increasing their rate of hospitalizations for eCOPD than those with higher levels of PA.

The quality of information about the impact of PA on patients with COPD has been growing. Pitta *et al.*[16] showed that COPD patients spent 64% of the time sitting or lying down, and only 6% walking, while healthy individuals spent 46% of their time sitting or lying down, and 11% walking. Tools such as questionnaires,[29] pedometers[30] and accelerometers[16,31,32] have demonstrated that COPD patients

Table 4 Multivariate Poisson regression with frequency of hospitalizations for COPD from 2 to 5 years after study enrolment as the response variable and covariates that could influence in the rate of hospitalizations

Covariate	Beta	SD	*P*	Exp (Beta) = OR	95% CI
Change in PA‡:					
1	0.643	0.284	0.024	1.901	(1.090–3.317)
2	0.911	0.313	0.004	2.488	(1.346–4.597)
3	0.631	0.295	0.039	1.879	(1.053–3.353)
4	0.411	0.313	0.188	1.509	(0.817–2.786)
5	0.167	0.362	0.645	1.181	(0.581–2.401)
6	0.758	0.318	0.017	2.134	(1.146–3.977)
7†	—	—	—	—	—
Hospitalizations for COPD exacerbations in the 2 years prior to enrolment					
0†	—	—	—	—	—
1	0.602	0.210	0.004	1.825	(1.210–2.752)
>1	0.803	0.267	0.003	2.231	(1.322–3.765)
Hospitalizations for COPD exacerbations in the first 2 years after enrolment					
0†	—	—	—	—	—
1	0.677	0.278	0.015	1.967	(1.142–3.391)
>1	0.849	0.268	0.002	2.337	(1.381–3.954)
Age	0.026	0.011	0.017	1.026	(1.005–1.048)
FEV_1%	–0.015	0.007	0.028	0.985	(0.972–0.998)

All patients with follow-up at 2 years after enrolment where included in the sample ($n = 428$). The time period to estimate the number of hospitalizations was calculated as the period between the two visits for patients with complete follow-up (324 patients) and as the period between the visits at 2 years after enrolment and the date of death or the date of withdrawal for deceased and excluded (24 and 80 patients respectively).

† Reference category.

‡ Coding for change in physical activity is the following:

1 = nr-PA (non regular walkers) to nr-PA/low.

2 = Low to nr-PA or moderate to nr-PA/low.

3 = Low to low.

4 = nr-PA/low to moderate/high or moderate to high.

5 = Moderate to moderate.

6 = High to nr-PA/low/moderate.

7 = High to high (reference).

—, 95% CI; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eCOPD, COPD exacerbation; FEV_1, forced expiratory volume in 1 s; nr-PA, non-regular physical activity; OR, odds ratio; PA, physical activity; SD, standard deviation.

Table 5 Estimated odds ratio for the rate of hospitalizations depending on the change in physical activity, adjusted by FEV_1% predicted, age, and hospitalizations for COPD exacerbations in the 2 years prior to enrolment and the first 2 years after enrolment

	Physical activity 2 years after enrolment				
Physical activity at baseline	nr-PA	Low: ≤3 km/day	Moderate: >3 and ≤6 km/day	High: >6 km/day	Working/sports
nr-PA	1.9 (1.1–3.3)				
Low: ≤3 km/week		1.9 (1.1–3.4)		1.5 (0.8–2.8)	
Moderate: >3 and ≤6 km/week	2.5 (1.3–4.6)		1.2 (0.6–2.4)		
High: >6 km/week	2.1 (1.1–4.0)			1	
Working/sports					

For each cell, number of patients, estimated odds ratio (highlighted) and 95% confidence intervals are shown. Patients maintaining the highest level of physical activity during the 3-year period were considered as a reference. Cells in white show no statistical significant difference and cells in grey show statistical significant difference with the reference category. Three shades of grey were used for statistical significance: light ($0.01 \le P < 0.05$), medium ($0.001 \le P < 0.01$) and dark ($P < 0.001$).

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; nr-PA, non-regular physical activity.

engage in less PA than healthy people of the same age.

The level of PA appears to have a direct impact on COPD outcomes such as hospitalizations and mortality.[33,34] In a cross-sectional, 1-year study of 340 patients, Garcia-Aymerich *et al*.[18] demonstrated that engaging in a high level of PA (232 kcal/day, the equivalent of walking for 60 min) was associated with fewer eCOPD-related hospitalizations compared with patients who expended less than 79 kcal/day in walking. Unlike our study, which only considered hospitalizations for eCOPD, Garcia-Aymerich included other diseases like pneumonia as causes of hospitalizations. In a population-based cohort study, the same group showed that patients with even relatively low levels of PA (e.g. walking or pedalling for 2 h/week) had a 28% lower risk of eCOPD hospitalization than those with little or no PA.[17] They did not, however, observe a dose-related response between the level of PA and hospitalizations or respiratory mortality.

In a cohort from the National Emphysema Treatment Trial, PA was an independently related prediction factors for hospitalization; engaging in ≥2 h/week of PA, as self-reported by patients, was associated with a reduction in hospitalizations.[35] When we used the classification of PA from that study in our cohort, we found that the great majority of the cohort was placed in the highest level of PA (>4 h/week), making any kind of analysis difficult. That was probably related to the greater severity of the National Emphysema Treatment Trial study cohort (mean FEV_1 of 27%). In other words, our patients were more physically active, and the protective effect of PA against eCOPD hospitalization in our cohort could be found in all severity levels of COPD, not only in the most severe patients. By using accelerometers, Garcia-Rio *et al*. have shown that PA was an independent prognostic factor for hospitalizations due to severe eCOPD with a linear dose–response relationship. In addition, in that study, the time to the first hospitalization due to eCOPD was shorter for the patients with lower levels of PA.[36]

The mechanism by which PA may prevent or reduce hospitalizations during eCOPD could be related to the capacity of PA to decrease systemic inflammation, as expressed by markers like C-reactive protein and tumour necrosis factor. Besides, PA may also have a local effect on pulmonary physiology, leading to better diffusing capacity of the lung carbon monoxide, reflecting more efficient pulmonary gas exchange and an improvement of maximal expiratory pressure as a marker of respiratory muscle strength.[37] Respiratory muscle strength had a positive correlation with maximal voluntary ventilation.[38] Maximal voluntary ventilation reflects the amount of available ventilatory reserve, which is used to supply increased demand during PA and possibly during eCOPD as well. In fact, maximal voluntary ventilation more strongly correlates with PA than do other functional variables such as FEV_1 or inspiratory capacity. In contrast, dynamic hyperinflation, which has been associated with limitations in PA,[39] contributes to respiratory muscle fatigue.[40] How regular PA is related to diffusing capacity of the lung carbon monoxide and improves maximal expiratory pressure and if it has any role in improving maximal voluntary ventilation is, however, currently speculative.

The strengths of our study include the large size of the cohort from general outpatient clinics, and a 5-year follow-up. We also conducted statistical adjustments with the intention to prevent confounding factors from biasing the outcomes of the study.

Our study has some limitations. We used a questionnaire to establish the level of PA instead of a direct measure like an accelerometer or pedometer. These self-reports of PA could lead to an overestimation or underestimation of the level of PA. Walking was used as the main measure of PA, and the time spent doing other activities, like housework, was not included. It is possible that other types of PA may influence eCOPD, but walking is by far the most usual form of PA during spare time in our environment. Analysis includes all the patients that survived in the first 2 years period of follow-up, even though some may have died during the next 3 years of follow-up, including for them the period time until death and the hospitalizations in that period of time. Patients who died during the first 2 years of follow-up period had been hospitalized more often for eCOPD and had a baseline PA lower than those who survived. This biases the results, which are based on survivors, as obviously, we were not able to examine the changes in PA for the patients that had not survived the selected period of time to measure it. As reverse causation and confounding are possible in this study, no causality or directionality of the findings can be inferred. Our patient cohort was almost exclusively composed of men (97%), reflecting the distribution of COPD in Spain.

In conclusion, we showed that patients who maintained a low level of PA or who decreased their PA level over time were more prone to have a significant increase in the rate of hospitalization for eCOPD. Increasing the level of PA or maintaining a moderate or high level of PA over time in a low-intensity activity, such as walking for at least 3–6 km/day, can reduce the number of eCOPD hospitalizations, regardless of the baseline level of PA. This suggests that small changes in PA habits could significantly improve an important outcome as hospitalization during eCOPD in those patients.

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REFERENCES

1 Miravitlles M, Mayordomo C, Artés M, Sánchez-Agudo L, Nicolau F, Segú JL, on the behalf of the EOLO Study Group. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. *Respiration* 2000; **67**: 495–501.

2 Donalson GC, Seemungal TAR, Patel IS, Lloyd-Owen SJ, Wilkinson TMA, Wedzicha JA. Longitudinal changes in the nature, severity and frequency of COPD exacerbations. *Eur. Respir. J.* 2003; **22**: 931–6.

3 Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W *et al.*; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 2010; **363**: 1128–38.

4 Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; **57**: 847–52.

5 Miravitlles M, Murio C, Guerrero T, Gisbert R. Costs of chronic bronchitis and COPD: a 1-year follow-up study. *Chest* 2003; **123**: 784–91.

6 Miller JD, Foster T, Boulanger L, Chace M, Russell MW, Marton JP, Menzin J. Direct costs of COPD in the U.S.: an analysis of Medical Expenditure Panel Survey (MEPS) data. *COPD* 2005; **2**: 311–8.

7 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**: 925–31.

8 Aaron SD, Vandemheen KL, Clinch JJ, Ahuja J, Brison RJ, Dickinson G, Hébert PC. Measurement of short-term changes in dyspnea and disease-specific quality of life following and acute COPD exacerbation. *Chest* 2002; **121**: 688–96.

9 Miravitlles M, Ferrer M, Pont A, Zalacaín 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**: 387–95.

10 Esteban C, Quintana JM, Moraza J, Aburto M, Egurrola M, España PP, Pérez-Izquierdo J, Aguirre U, Aizpiri S, Capelastegui A. Impact of hospitalisations for exacerbations of COPD on health-related quality of life. *Respir. Med.* 2009; **103**: 1201–8.

11 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.): S351–8.

12 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**: 1093–8.

13 Sari N. Physical inactivity and its impact on healthcare utilization. *Health Econ.* 2009; **18**: 885–901.

14 Sari N. A short walk a day shortens the hospital stay: physical activity and the demand for hospital services for older adults. *Can. J. Public Health* 2010; **101**: 385–9.

15 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**: 716–25.

16 Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2005; **171**: 972–7.

17 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**: 772–8.

18 Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003; **58**: 100–5.

19 From the global strategy for the diagnosis, management and prevention of COPD; Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. [Accessed 22 January 2014.] Available from URL: http://www.goldcopd.org/

20 Sanchis J. Normativa para la espirometría forzada: Grupo de trabajo de la SEPAR para la práctica de la espirometría clínica. *Arch. Bronconeumol.* 1989; **25**: 132–42.

21 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.

22 Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959; **2**: 257–66.

23 Ware JE, Snow KK, Kosinsky M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. The Health Institute, Boston, 1993.

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

25 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**: 1087–94.

26 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**: 1160–6.
27 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 1987; **40**: 373–83.
28 ATS statement. Guidelines for the six-minute walk test. *Am. J. Respir. Crit. Care Med.* 2003; **167**: 211–77.
29 Garcia-Aymerich J, Félez MA, Escarrabill J, Marrades RM, Morera J, Elosua R, Antó JM. Physical activity and its determinants in severe chronic obstructive pulmonary disease. *Med. Sci. Sports Exerc.* 2004; **36**: 1667–73.
30 Schönhofer B, Ardes P, Geibel M, Köhler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. *Eur. Respir. J.* 1997; **10**: 2814–9.
31 Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. *Eur. Respir. J.* 2009; **33**: 262–72.
32 Watz H, Waschki B, Boehme C, Claussen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. *Am. J. Respir. Crit. Care Med.* 2008; **177**: 743–51.
33 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**: 458–63.
34 Waschki B, Kirsten A, Holz O, Müller KC, Meyer T, Watz H, Magnussen H. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011; **140**: 331–42.
35 Benzo RP, Chang CC, Farrell MH, Kaplan R, Ries A, Martinez FJ, Wise R, Make B, Sciurba F, National Emphysema Treatment Trial Research Group. Physical activity, health status and risk of hospitalization in patients with severe chronic obstructive pulmonary disease. *Respiration* 2010; **80**: 10–8.
36 Garcia-Rio F, Rojo B, Casitas R, Lores V, Madero R, Romero D, Galera R, Villasante C. Prognostic value of the objective measurement of daily physical activity in COPD patients. *Chest* 2012; **142**: 338–46.
37 Garcia-Aymerich J, Serra I, Gómez FP, Farrero E, Balcells E, Rodríguez DA, de Batlle J, Gimeno E, Donaire-Gonzalez D, Orozco-Levi M *et al.* Phenotype and Course of COPD Study Group. Physical activity and clinical and functional status in COPD. *Chest* 2009; **136**: 62–70.
38 Pitta F, Takaki MY, Oliveira NH, Santanna TJ, Fontana AD, Kovelis D, Camillo CA, Probst VS, Brunetto AF. Relationship between pulmonary function and physical activity in daily life in patients with COPD. *Respir. Med.* 2008; **102**: 1203–7.
39 Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, López-Collazo E, Alvarez-Sala R. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. *Am. J. Respir. Crit. Care Med.* 2009; **180**: 506–12.
40 O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerant in chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 2006; **3**: 180–4.