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Physical Activity Is Associated with Attenuated Disease Progression in COPD

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ABSTRACT

Introduction: COPD progression is variable and affects several disease domains, including decline in lung function, exercise capacity, muscle strength and health status as well as changes in body composition. We aimed to assess the longitudinal association of physical activity (PA) with these *a priori* selected components of disease progression. **Method:** We studied 114 COPD patients from the PAC-COPD cohort [94% male, mean (SD) 70 (8) years of age, 54 (16) FEV_1 % predicted] at baseline and 2.6 (0.6) years later. Baseline PA was assessed by accelerometry. Multivariable general linear models were built to assess the association between PA and changes in lung function, functional exercise capacity, muscle strength, health status and body composition. All models were adjusted for confounders and the respective baseline value of each measure. **Results:** Per each 1000 steps higher baseline PA, FEV_1 declined 7 ml less ($p<0.01$), FVC 9 ml less ($p=0.03$) and carbon monoxide diffusing capacity 0.10 ml/min/mmHg less ($p=0.04$), while the St George's Respiratory Questionnaire (SGRQ) symptom domain deteriorated 0.4 points less ($p=0.03$), per year follow-up. PA was not associated with changes in functional exercise capacity, muscle strength, other domains of health status or body composition. **Conclusion:** Higher PA is associated with attenuated decline in lung function and reduced health status (symptoms domain) deterioration in moderate-to-very severe COPD patients.

Key words: Longitudinal analysis; lung function; muscle strength; health status; exercise capacity

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has been considered a progressive disease characterized by accelerated lung function decline. Recent research indicates that the natural course of COPD is heterogeneous since lung function may remain stable over time in a sizable proportion of patients (1). In addition, deterioration in other important elements of the disease such as exercise capacity, skeletal muscle strength, health status or body composition can occur (2-5) and influence survival (6-9). A better understanding of the determinants of disease progression, a multi-dimensional composite that goes beyond lung function, can become critical to prevent it.

Previous research has shown that COPD key features are themselves the best predictors of disease progression. Thus, level of airflow limitation, presence of exacerbations, dyspnoea severity and presence of underlying emphysema have been associated with faster lung function decline and other dimensions of disease progression (1,2,4,10-12). Consequently, some therapeutic interventions aim to reverse or prevent the patients' worsening by targeting the determinants alluded to (13). Surprisingly, apart from smoking (1), behavioural factors that are potentially associated with COPD progression are ill-defined. The latter is vital as these factors could subsequently be translated into interventions.

We hypothesized that physical activity (PA), known to be associated with the risk of two important components of disease progression, namely exacerbations and all-cause mortality (14), is associated to several components of the disease progression. Regrettably, previous studies are meagre, mostly cross-sectional and PA is often measured using questionnaires, thus subject to misclassification (14). A recent longitudinal study using accelerometry showed that persistent inactivity (i.e. severe inactivity both at baseline and follow-up) was associated with a faster 3-years decline in functional exercise capacity and in fat free mass (5). However, this study approach, as indicated by the investigators, could not discard reverse causation, this is that decline in some functional outcomes is in fact the cause, and not the consequence, of persistent inactivity. Moreover, from a clinical viewpoint, to identify whether PA at a given time point is related to a future decline in the outcomes alluded to, is of utmost importance to apply appropriate secondary preventive strategies, a goal not aimed for in the latter study.

Therefore, in the present study, we investigate the association between objectively measured PA with disease progression (which we *a priori* defined as changes in lung function, functional exercise capacity, muscle strength, health status, and body composition) in a large cohort of well characterized COPD patients (PAC-COPD) (15,16). We hypothesized that higher physical activity at baseline would be positively associated with a lower decline in lung function, functional exercise capacity and muscle strength and with decreased body mass and increased fat free mass indexes as well.

METHODS

A complete description of the methods used is presented in the online supplement [see Appendix, Supplemental Digital Content 1, Methods, http://links.lww.com/MSS/B462].

Patient population and design

This longitudinal study is based on the population of the "Phenotype and Course of COPD (PAC-COPD)" study described elsewhere (15,16). A total of 177 patients, representative for the full PAC-COPD cohort (17), had a measurement of physical activity (PA) by accelerometry, 18 to 24 months after inclusion (herein referred to as baseline) and were considered for the present analysis. Among these 177 patients, a total of 114 patients participated in the next clinical visit with a mean (SD) follow-up of 2.6 (0.6) year (follow-up visit of the present paper) and were included in the analyses. Patients who dropped out (n=63) showed generally a worse functional status at baseline than patients followed-up (see Table, Supplemental Digital Content 2, Baseline characteristics of COPD patients according to follow-up status, http://links.lww.com/MSS/B463). The study was approved by the Ethics Committee of participating hospitals and all patients signed their informed consent.

Physical activity and outcomes

PA was measured by the Sensewear PRO armband (Body Media, Pittsburgh, PA, USA), previously validated in COPD patients (18), at baseline and during follow-up. Patients were asked to wear the monitor during 7 consecutive days. Waking hours (from 8AM to 10PM) were

selected and a valid measurement was defined *a priori* as at having at least 3 days of measurement with at least 70% of wearing time of the waking hours (19). We obtained the total daily step count, time in moderate-to-vigorous PA (MVPA), and sedentary time.

Both at baseline and during follow-up (15) we assessed *(1)* post-bronchodilator forced spirometry [forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)] and lung diffusing capacity for carbon monoxide (DL_{co}); *(2)* functional exercise capacity by the 6-min walk distance (6MWD); *(3)* muscle strength by the hand grip force of the non-dominant hand (HGF) and maximal inspiratory (MIP) and expiratory pressures (MEP); *(4)* health status by the Saint George's Respiratory Questionnaire (SGRQ); and *(5)* body composition expressed as body mass index (BMI), fat free mass (FFM) and FFM index (FFMi), measured by bioelectrical impedance. We calculated the annual rate of change as the difference between the two measurements divided by the follow-up time, in each individual patient.

Other measurements

As reported elsewhere (15) socio-demographic and other clinical data were collected at baseline. Mean number of daylight hours during the week of the PA measurement was calculated (19). The number of hospitalizations and/or visits to the emergency room for respiratory problems during follow-up was obtained from national administrative databases.

Statistical analysis

Sample size calculations and treatment of missing data (multiple imputation through chain equations) are detailed in the supplement (see Table, Supplemental Digital Content 3, Baseline characteristics of patients using complete cases and imputed data set, http://links.lww.com/MSS/B464). Table, Supplemental Digital Content 3, shows patients characteristics of the complete case and the imputed population. Data are presented as mean (SD) or median [25^{th}-75^{th} percentile]; categorical variables are presented as n (%). First, we tested the association between each PA exposure (i.e. step count, MVPA and sedentary time) and outcomes, adjusted for the baseline values of the corresponding outcome. Second, we built multivariable general linear models adjusted for baseline levels of the outcome and potential

confounders (details in the Supplemental Digital Content and tables' footnotes). We tested goodness of fit in all models.

Additional analyses included: (i) stratification of final models by smoking status; (ii) stratification of sedentary time models by MVPA median levels; (iii) inclusion of the variable "exacerbations during follow-up" (≥1 vs. 0) in the final model to test whether the association was mediated by an effect of PA on exacerbations; and (iv) comparing disease progression between patients who were persistently inactive, persistently active and activity decliners, to allow comparison with the paper by Waschki et al(5). Finally, as sensitivity analyses, we *(1)* excluded subjects with extreme values in the accelerometer measurements; and, *(2)* repeated the multivariable analyses using linear mixed models and *(3)* excluded patients who were participating in a pulmonary rehabilitation program.

RESULTS

Patient characterization

Patient characteristics are shown in Table 1. Patients wore the accelerometer for a mean (SD) of 6 (1) days for 89 (9) % of the daytime hours. Only 4% of patients were participating in a pulmonary rehabilitation program. At baseline they walked 7362 (4589) steps.day^{-1}. After 2.6 (0.6) years of follow-up there was a moderate, albeit statistically significant, highly variable decline in most outcomes of interest [mean change of FEV_1 -24.2 ml.year^{-1}, 6MWD -7.7 m.year^{-1}, HGF -7.8 N.year^{-1}, total SGRQ +1.44 points.year^{-1} and FFM -0.48 kg.year^{-1}] (Table 2).

Relationship between PA and disease progression

Figure 1 and 2 show that baseline daily step count was significantly associated with slower decline in FEV_1, FVC, DL_{CO} and SGRQ symptoms score during follow-up, but not significantly with lower decline in 6MWD and MIP, all adjusted for the respective baseline values. By contrast, no associations between baseline step count and change in body composition outcomes were observed.

After adjusting for confounders (see Tables' footnote), per each 1000 steps of more PA at baseline, patients declined 7 ml less FEV_1 per year ($p<0.01$), 9 ml less FVC per year ($p=0.03$) and 0.10 ml/min/mmHg less DL_{co} per year ($p=0.04$); similarly, they increased 0.4 points less ($p=0.03$) in the SGRQ symptom domain per year (Table 3). Associations with other outcomes were not statistically significant [see Table, Supplemental Digital Content 4, Average annual change in exercise capacity, respiratory muscle force and other domains of health status related to baseline step count (multivariable linear regression model, http://links.lww.com/MSS/B465)]. Bivariate associations were similar with MVPA [see Figure, Supplemental Digital Content 5, Patients' annual change in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline moderate-to-vigorous physical activity (MVPA) levels (quartiles), http://links.lww.com/MSS/B466] or sedentary time [see Figure, Supplemental Digital Content 6, Patients' annual change in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline sedentary time levels (quartiles), http://links.lww.com/MSS/B467]. After adjusting for confounders (see footnotes), more time in MVPA was associated with lower decline in FEV_1 and FVC, and higher sedentary time was related to worsening of FEV_1, FVC, DL_{co} and SGRQ symptoms score (Table 3). Linear regression goodness of fit tests did not reveal any abnormality.

Additional and sensitivity analyses

Stratification of PA models based on baseline smoking status showed a stronger association between PA and FEV_1 decline in active smokers so, per each additional 1000 steps, smokers declined FEV_1 by 11.0 (4.2) ml per year less (vs. 4.6 (3.2) ml per year in former smokers, p-value for interaction=0.06). This effect modification was not observed for the other outcomes. Stratification of sedentary time models according to patients' MVPA level did not show any relevant effect modification [see Table, Supplemental Digital Content 7, Average annual change in lung function and symptoms domain of health status related to baseline sedentary time (multivariable linear regression model), according to baseline moderate-to-vigorous physical activity (MVPA), http://links.lww.com/MSS/B468]. Forty-three percent of patients had at least one exacerbation (severe and/or moderate) during follow-up. The inclusion of this variable in the multivariable models did not change the associations (see Table, Supplemental Digital Content 8, Average annual change in lung function and symptoms domain of health status related to

baseline step count, with and without having exacerbations during follow-up as a covariate, http://links.lww.com/MSS/B469).

The subgroup of patients (n=92) with PA data at both time points declined from 7734 (4621) to 5857 (4059) steps.day^{-1} ($p<0.001$). When dividing these patients into persistently inactive, persistently active and PA decliners [see Figure, Supplemental Digital Content 9, Patients' annual change in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to physical activity changes status (persistently active, decliners and persistently inactive), http://links.lww.com/MSS/B470], while emulating the methodology by Waschki (5), the declines in FEV_1, FVC, DL_{co} and $SGRQ_{symptom}$ domain were faster in persistently inactive than in persistently active patients. The other outcomes did not significantly differ.

Sensitivity analyses yielded very similar results. See:

- Table, Supplemental Digital Content 10, Average annual change in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable linear regression model) after excluding extreme values of physical activity variables, http://links.lww.com/MSS/B471
- Table, Supplemental Digital Content 11, Average annual change in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable mixed model), http://links.lww.com/MSS/B472
- Table, Supplemental Digital Content 12, Average annual change in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable linear regression model) after excluding patients participating in a pulmonary rehabilitation program at baseline (n=4), http://links.lww.com/MSS/B473.

DISCUSSION

This study shows that PA is associated with attenuated 2-3 years deterioration of some (lung function and symptoms domain of health status) relevant components of disease progression, after adjusting for confounders, and irrespective of their baseline values.

The most novel finding is the association between PA and lung function decline. This is in variance with a previous study that found a weak but significant correlation ($r=0.24$, $p=0.04$), but did not retain PA as an independent predictor of FEV_1 decline (20) and the observation that persistent inactivity was not related to lung function changes (5). Since patients of the latter study had similar characteristics, the same accelerometer was used and that we emulated their statistical approach, we suggest that a residual confounding effect could contribute to explain this discrepancy. In line with evidence in the general population (21), we found a stronger association in active smokers, pointing to biological mechanisms shared by PA and smoking in their association with lung function decline. Finally, to our knowledge, no previous longitudinal study has assessed the relationship between PA and DL_{co} in COPD, albeit a positive cross-sectional association was found based on the PAC-COPD study (22) and DL_{co} was shown to be a related to PA in (ex-) smokers with airflow obstruction (23).

Several, non-mutually exclusive, mechanisms can contribute to explain the observed association between PA and lung function decline: *(1)* PA can have an anti-inflammatory or anti-oxidant effect (21,24-26) likewise, *(2)* PA might theoretically reduce the frequency of COPD exacerbations(14) which, in turn, preserves lung function (27) and health status (28). However, our results do not support this contention (see Table, Supplemental Digital Content 8, Average annual change in lung function and symptoms domain of health status related to baseline step count, with and without having exacerbations during follow-up as a covariate, http://links.lww.com/MSS/B469); and finally (3) PA can influence respiratory muscle strength. However, this is likely a less important contributor in COPD patients because the relationship between respiratory muscle strength and lung function is weak (29) and increases in strength do not lead to changes in lung function (30).

As a second relevant finding, we found that PA was associated with lower health status (symptoms domain) worsening, in agreement with previous reports (14). Surprisingly, PA was not associated with changes in the SGRQ activity domain. It is of note that the activity domain

refers to ‘activities that cause or are limited by breathlessness’. This lack of association may be therefore in line with previous studies showing that the amount of PA and experienced difficulties with PA are distinct concepts (31).

Finally, we did not find an association between PA and changes in functional exercise capacity, muscle strength or body composition outcomes. Although PA relates cross-sectionally to these outcomes, research on their association over time is scarce (5,22,32). A previous study found a faster decline in functional exercise capacity and FFM in persistently inactive patients (5). That the functional decline in our cohort was slightly slower might have limited our ability to identify differences, albeit the magnitude of this association is estimated to be small [see Table, Supplemental Digital Content 4, Average annual change in exercise capacity, respiratory muscle force and other domains of health status related to baseline step count (multivariable linear regression model), http://links.lww.com/MSS/B465]. Because the modification of functional exercise capacity and muscle strength require regularly scheduled intense activities (33) and that activities of daily living are generally of low intensity, a lack of association may be conceivable. In fact, a previous study that found a relation between PA and functional exercise capacity decline used the self-reported ‘hard activity’ as PA measurement (32). Moreover, like in previous studies (14), we did not have available data on quadriceps muscle strength so, regrettably, whether PA is associated with this decline could not be explored. Because this muscle is often affected in COPD (34), while other can still be preserved, future studies aiming to investigate the association between PA and muscle strength should consider including quadriceps muscle strength in the analysis.

Potential clinical implications

First, while we acknowledge that any clinically meaningful preservation of lung function requires a large increase in PA, the modest association for every 1000 steps is somehow comparable to the effect of pharmacotherapy on FEV_1 decline, ranging between 2 and 16 ml/year of less decline in the treatment arm compared with the placebo one (35,36). In this context it is also important to note that an increase of 1000 steps is meaningful (37), feasible (38) and neither induce adverse events nor related costs. Second, smoking cessation is the key therapeutic intervention in patients with COPD with the greatest impact on the natural history of COPD and

the only behavioural factor that has been related to disease progression. The ECLIPSE study showed a 21 ml greater annual decline in FEV_1 in current smokers compared with non-smokers (1). The attenuation seen for every 1000 steps of more physical activity can thus in magnitude be seen as a third of the effect observed by smoking cessation, an effect with no doubt of clinical relevance. Third, most importantly, the observed benefits of PA occurred on top of the pharmacologic treatment (69% of patients used combination therapy, see Table 1) regardless of smoking behaviour. Fourth, the fact that PA relates to DL_{co} decline may be clinically relevant since DL_{co} is an excellent functional marker of pulmonary emphysema and a strong mortality predictor in COPD (39). DLco is an important functional marker of disease progression with a prognostic value higher than that of airflow limitation (40), is a sign of arterial oxygen desaturation during exercise and relates to the decline in exercise performance (41). Finally, along with previous research, a proportion of patients remained stable over time (1). The current results suggest that different PA levels can contribute to explain the heterogeneity of COPD progression (1).

Our results provide relevant information for future research, particularly for the selection of PA parameters. First, using MVPA resulted in similar results than step count but it was of lower magnitude and less statistical power. We suggest that future studies aiming to assess the effects of PA in chronically diseased subjects like COPD should focus on parameters of "light" PA, as previously proposed (19,42). Second, we assessed PA and sedentary time independently, as well as their interaction, based on previous research in healthy individuals (43). PA and sedentary time rendered similar results (although of opposite direction) in their association with COPD progression, hence representing a similar concept in this population.

Strengths and limitations

Our study has several strengths: *(1)* This is one of the first studies analysing the longitudinal association between objectively measured PA and several *a priori* selected components of disease progression; *(2)* it considers potential confounders by investigating an extensively well identified cohort (PAC-COPD), thus minimizing confounding; and finally, *(3)* by following patients longitudinally and including the baseline values of each outcome in the multivariable models, the potential of reverse causation (i.e., that the outcomes decline leads to a lower PA) as

an additional explanation of our findings is reduced. Our study, however, also has shortcomings: *(1)* the analysis was restricted to 33% of the original cohort. Although these patients were found representative for the entire cohort (17), survival bias might have influenced the present estimates because patients who were lost for follow-up had a worse overall status at baseline (see Table, Supplemental Digital Content 2, Baseline characteristics of COPD patients according to follow-up status, http://links.lww.com/MSS/B463). The most likely consequence, though, is underestimation of the observed associations because lost patients are expected to have a faster decline; *(2)* the sample of 114 patients represents a relatively large cohort in terms of objectively measured PA but it is a modest sample to investigate decline in outcomes with large (biological) variability so the lack of statistical power could potentially have caused lack of statistical significant results for some outcomes (e.g. 6MWD); *(3)* based on expert opinion, the estimate in decline traditionally relies on more frequent data collection. Our study is limited by two measures, with a mean of 2.6 years apart; *(4)*the results based on the current population, with a majority of male patients, cannot be directly extrapolated and need to be confirmed; and *(5)* The physical activity of the present cohort is higher than that observed in previous studies, which could be considered a limitation. However, when comparing clinical characteristics and physical activity of the present cohort and previous studies, differences can be seen among countries (for a similar severity of COPD) as well as within countries (differences in disease severity and/or setting). In addition, the present sample has a high proportion of male subjects (reflecting the COPD gender distribution in Spain), which could have also contributed to the higher physical activity.

CONCLUSIONS

This study shows that increased PA is associated with attenuated decline in lung function and reduced deterioration of the symptoms domain of health status (but not to changes in functional exercise capacity, muscle strength, other domains of health status or body composition) in patients with moderate-to-very severe COPD.

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FIGURES

Figure 1: Patients' annual change* in outcomes of COPD progression [lung function (panel a-c), functional exercise capacity (panel d) and muscle strength (panel e-g)] during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline physical activity (step count) levels.

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{CO} = diffusion capacity of the lung carbon monoxide, 6MWD= 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure.

* Negative values represent a decline in the outcome measure.

Data presented as estimated marginal means (Least squares means) and SEM, adjusted for the baseline of the outcome of interest. Patients were divided in 4 groups based on the mean baseline step count: Active (≥10000 steps.day^{-1}, n=23), somewhat active (7500-10000 steps.day^{-1}, n=31), inactive (5000-7500 steps.day^{-1}, n=23) and very inactive (<5000 steps.day^{-1}, n=37). P-values indicate p-for-trend.

Figure 2: Patients' annual change* in outcomes of COPD progression [health status (panel a-d) and body composition (panel e-g)] during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline physical activity (step count) levels.

SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi= fat free mass index.

* Negative values represent a decline in the outcome measure.

Data presented as estimated marginal means (Least squares means) and SEM, adjusted for the baseline of the outcome of interest. Patients were divided in 4 groups based on the mean baseline step count: Active (≥10000 steps.day^{-1}, n=23), somewhat active (7500-10000 steps.day^{-1}, n=31), inactive (5000-7500 steps.day^{-1}, n=23) and very inactive (<5000 steps.day^{-1}, n=37). P-values indicate p-for-trend.

Supplemental digital content

SDC 1—Appendix 1. Methods (complete version) http://links.lww.com/MSS/B462

SDC 2—Supplementary Table 1. Baseline characteristics of COPD patients according to follow-up status. http://links.lww.com/MSS/B463

SDC 3—Supplementary Table 2. Baseline characteristics of patients using complete cases and imputed data set http://links.lww.com/MSS/B464

SDC 4—Supplementary Table 3. Average annual change in exercise capacity, respiratory muscle force and other domains of health status related to baseline step count (multivariable linear regression model) http://links.lww.com/MSS/B465

SDC 5—Supplementary Figure 1. Patients' annual change in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline moderate-to-vigorous physical activity (MVPA) levels (quartiles). http://links.lww.com/MSS/B466

SDC 6—Supplementary Figure 2. Patients' annual change in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline sedentary time levels (quartiles) http://links.lww.com/MSS/B467

SDC 7—Supplementary Table 4. Average annual change in lung function and symptoms domain of health status related to baseline sedentary time (multivariable linear regression model), according to baseline moderate-to-vigorous physical activity (MVPA) http://links.lww.com/MSS/B468

SDC 8—Supplementary Table 5. Average annual change in lung function and symptoms domain of health status related to baseline step count, with and without having exacerbations during follow-up as a covariate http://links.lww.com/MSS/B469

SDC 9—Supplementary Figure 3. Patients' annual change in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to physical activity changes status (persistently active, decliners and persistently inactive).

SDC 10—Supplementary Table 6. Average annual change in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical

activity (MVPA) at baseline (multivariable linear regression model) after excluding extreme values of physical activity variables

SDC 11—Supplementary Table 7. Average annual change in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable mixed model)

SDC 12—Supplementary Table 8. Average annual change in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable linear regression model) after excluding patients participating in a pulmonary rehabilitation program at baseline (n=4)

Figure 1

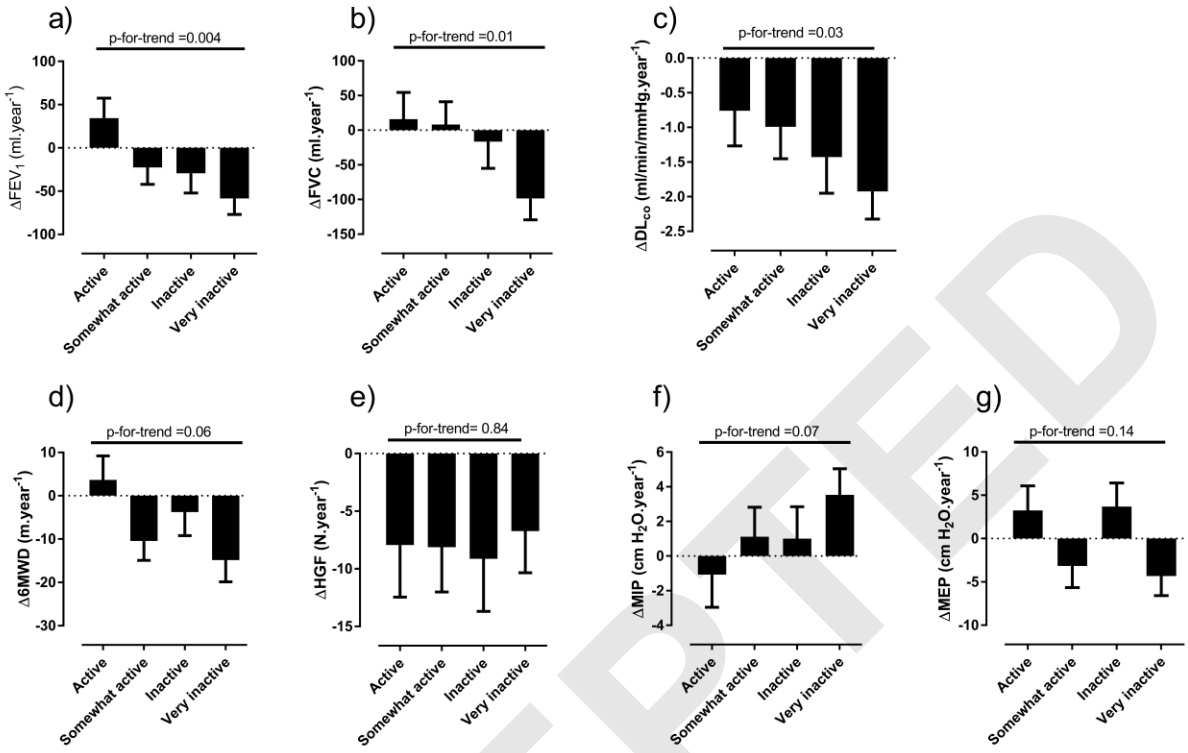

Figure 2

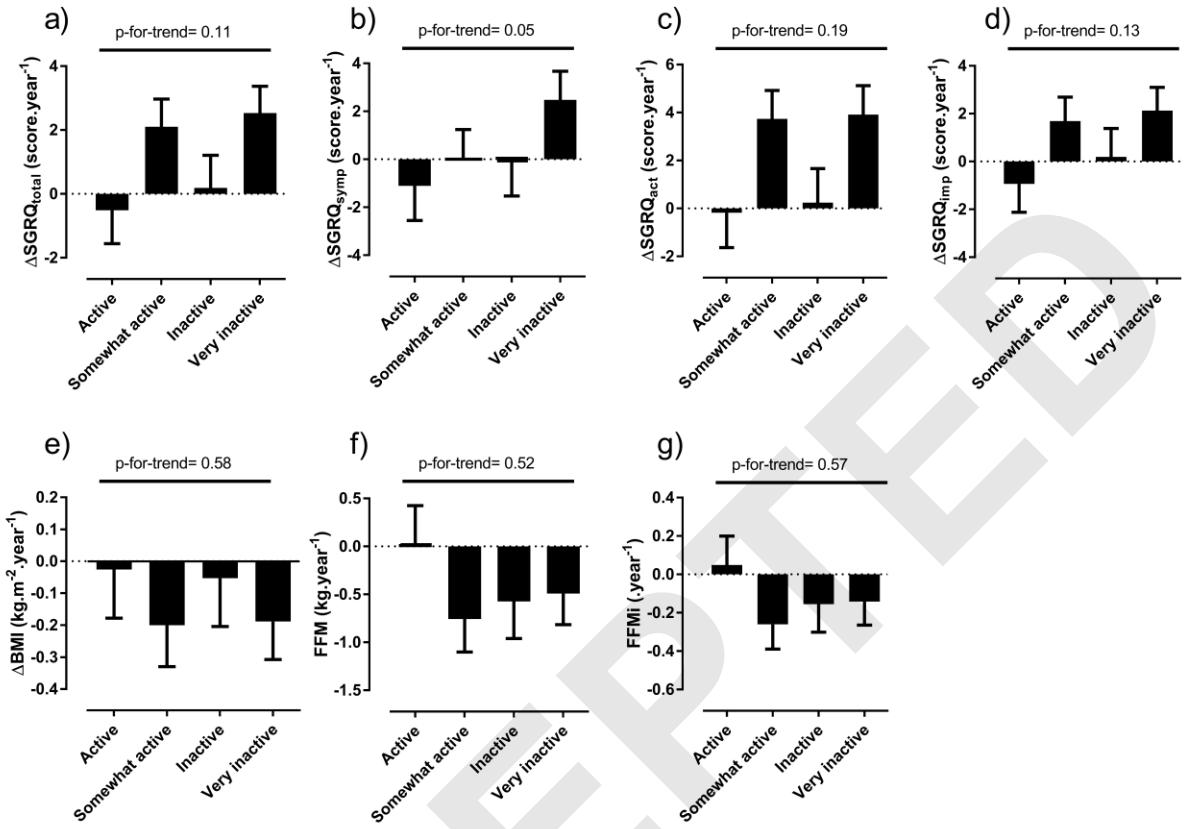

Table 1: Baseline characteristics of 114 COPD patients.

Sex: male	94%
Age (years)	70 (8)
Smoking status: active	30%
FEV_1 (% predicted)	54 (16)
FVC (% predicted)	72 (15)
DL_{co} (% predicted) [*]	66 (24)
mMRC (0/1/2/3/4)	21% /35% /23% /6% /15%
Spirometric severity (ATS/ERS I/II/III/IV)	6% / 59% / 27% / 8%
Working status: active [*]	9%
Charlson index ≥2	55%
Long acting bronchodilator therapy [ǂ]	85%
Inhaled corticosteroids therapy [‡]	74%
Combination inhaled therapy (long acting bronchodilator + inhaled corticosteroids)	69%
Participation in pulmonary rehabilitation	4%
≥1 COPD admission in the previous 12 months	11%
Step count ($n.day^{-1}$)	7362 (4589)
MVPA ($min.day^{-1}$)	52 [22-91]
Sedentary time ($min.day^{-1}$)	624 (118)
Physically very inactive (<5000 $steps.day^{-1}$)	37 (32)

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, mMRC = modified Medical Research Council dyspnea scale, MVPA = time in moderate-to-vigorous physical activity.

Data are presented as %, mean (SD) or median [25th-75th percentile], [*] Descriptive analyses conducted using imputed dataset in the case of missing data, [ǂ] Long acting muscarinic agents (LAMA) or long-acting beta agonists (LABA) alone or in combination with other inhaled

medications. ‡ Alone or in combination with other inhaled medications. Lung function results were expressed as a % of reference values of a Mediterranean population (Roca, bulletin européen de physiopathologie respiratoire, 1986; Roca, American Review of Respiratory Disease, 1990).

Table 2: COPD progression: average annual changes during a mean follow-up of 2.6 years.

	Baseline	*Follow-up*	*Decline (per year)*
FEV_1 (ml)	1620 (525)	1550 (563)	-24.2 (112) ǂ
FVC (ml)	2942 (651)	2849 (741)	-30.2 (189)
DL_{co} (ml/min/mmHg) *	16.4 (6)	13.0 (7)	-1.33 (3) ǂ
6MWD (m) *	411 (98)	389 (117)	-7.7 (27) ǂ
HGF (N)	295 (87)	272 (84)	-7.84 (23) ǂ
MIP (cm H_2O) *	-73 (28)	-68 (27)	1.44 (10)
MEP (cm H_2O) *	106 (38)	105 (37)	-0.87 (15)
SGRQ total score (points) *	29 (17)	33 (18)	1.33 (5) ǂ
SGRQ symptoms (points) *	26 (19)	28 (21)	0.58 (8)
SGRQ activity (points) *	42 (24)	48 (24)	2.30 (7) ǂ
SGRQ impacts (points) *	22 (16)	25 (18)	1.00 (6)
BMI ($kg.m^{-2}$)	29 (5)	29 (9)	-0.13 (0.72)
FFM (kg) *	55 (10)	54 (10)	-0.48 (1.9) ǂ
FFMi ($kg.m^{-2}$) *	19.9 (3)	19.6 (3)	-0.14 (0.8)

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, 6MWD= 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi= fat free mass index.

Data are presented as mean (SD), * Descriptive analyses conducted using imputed dataset in the case of missing data, ǂ Significant change over time ($p<0.05$).

Table 3: Average annual change* in lung function and symptoms domain of health status related to baseline step count, moderate-to-vigorous physical activity (MVPA) and sedentary time (multivariable linear regression model†).

	Step count		MVPA		Sedentary time	
	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value	Per 10 minutes.day^{-1} increase Estimate (95% CI)	p-value	Per hour.day^{-1} increase Estimate (95% CI)	p-value
ΔFEV_1 (ml.year^{-1})	7.26 (2.3 to 12.2)	<0.01	6.40 (2.9 to 10.0)	<0.01	-15 (-27 to -3)	0.02
ΔFVC (ml.year^{-1})	8.78 (0.7 to 16.9)	0.03	6.04 (0.3 to 12.0)	0.05	-20 (-40 to -1)	0.04
ΔDL_{co} (ml/min/mmHg.year^{-1})	0.10 (0.0 to 0.2)	0.04	0.03 (0.0 to 0.1)	0.40	-0.25 (-0.5 to 0.0)	0.06
$\Delta SGRQ_{symptoms}$score (points.year^{-1})	-0.36 (-0.7 to 0.0)	0.03	-0.19 (-0.4 to 0.0)	0.12	0.73 (0.0 to 1.5)	0.06

MVPA = time in moderate-to-vigorous physical activity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, SGRQ = Saint George's respiratory questionnaire.

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for baseline value of the corresponding outcome and (i) age, sex, exacerbation history (≥1 / 0), BMI, Charlson index, smoking status (current / not current), pack-years and duration of daylight for lung function variables, or (ii) age, sex, exacerbation history (≥1 / 0), smoking status, FEV1% predicted, 6MWD and duration of

daylight for SGRQ. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the online supplement

Physical activity is associated with attenuated disease progression in COPD

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Appendix 1: Methods (complete version)

Patient population and design

This study is based on the 'Phenotype and Course of Chronic Obstructive Pulmonary Disease (PAC-COPD) cohort (1). The PAC-COPD cohort consists of 342 patients with COPD (diagnosis based on post-bronchodilator spirometry under stable conditions established according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (2)) who were admitted for the first time for an exacerbation in nine participating hospitals in Spain. The PAC-COPD project is a prospective multicenter study aimed at investigating the phenotype heterogeneity of COPD. The main exclusion criteria were age under 45 years, severe comorbidities, general fragility and mental disability. A total of 177 patients, representative for the full PAC-COPD cohort (3), had a measurement of physical activity (PA) by accelerometry, 18 to 24 months after inclusion (herein referred to as baseline) and were considered for the present analysis. Among these 177 patients, 27 patients died, 36 were lost to follow-up and a total of 114 patients participated in the next clinical visit with a mean (SD) follow-up of 2.6 (0.6) year (follow-up visit of the present paper) and were included in the analyses. Patients who dropped out (n=63) showed generally a worse functional status at baseline than patients followed-up (see Supplementary Table 1). The study

was approved by the Ethics Committees of all the participating hospitals and patients gave written informed consent before any data collection.

Physical activity and outcomes

Physical activity was objectively measured at baseline and during follow-up using the Sensewear PRO armband (Body Media, Pittsburgh, PA, USA). This accelerometer has been thoroughly validated in patients with COPD (4,5). Patients were asked to wear the monitor on the right arm during 7 consecutive days. Waking hours (from 8AM to 10PM) were selected and a valid measurement was defined *a priori* as at having at least 3 days of measurement with at least 70% of wearing time of the waking hours (6). To account for seasonal variation, mean duration of daylight was calculated based on the date of the PA measurement using a latitude of 41.38°N (6). The mean number of daylight hours during the week of the measurement was obtained, as it is known to be associated with physical activity (6).

The accelerometer provides a minute-by-minute export (Sensewear 5.0 PRO software) including step count and the metabolic equivalent of tasks (METs). PA was expressed as the total number of steps per day and time in moderate-to-vigorous physical activity (MVPA), defined as any activity above 3 METs (7). These PA variables were based on all minutes the accelerometer had been worn. Mean step count was chosen as the primary exposure of the present paper. Sedentary time (ST) was defined as any activity below 1.5 METs during waking hours (from 8AM to 10PM) (7), to be in line with the current definition of sedentary behavior referring to waking hours (8). Therefore, to analyze sedentary time two patients working in shifts (including night work) were excluded. Because in the general population sedentary behavior has shown to be associated with worse health outcomes, irrespective of the PA level (9) and decreasing sedentary behavior could likely be a more realistic aim in COPD

patients since they are often highly inactive (10), we included sedentary time as secondary outcome.

The outcomes of interest were assessed during baseline and at follow-up. A detailed description of the measurement methodology has been published elsewhere. (1) The outcomes of interest included *(1)* lung function parameters [forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and diffusing capacity of the lung carbon monoxide (DL_{co})]. Baseline results were expressed as a % of reference values of a Mediterranean population. (11,12) ; *(2)* exercise capacity using the 6-min walk distance (6MWD); *(3)* muscle function as measured by the hand grip force of the non-dominant hand (HGF), maximal inspiratory (MIP) and expiratory pressure (MEP); *(4)* health status measured by the Saint George's Respiratory Questionnaire (SGRQ), including total score and the symptoms, activity and impact subdomains; and *(5)* body composition measured by body mass index (BMI), fat free mass (FFM) and FFM index (FFMi), measured by bioelectrical impedance (13) and calculated as FFM in kg/(height)^2, a surrogate of skeletal muscle mass. In each subject the annual change was calculated as the difference between the two measurements (absolute values) divided by the follow-up time. The annual changes of the parameters were chosen as the outcomes of interest.

Other measures

As reported elsewhere (1) sociodemographic data (including education and marital status), dietary habits, comorbidities (used to calculate the Charlson index), participation in a pulmonary rehabilitation program, smoking status and history, dyspnea using the modified Medical Research Council scale (mMRC) and number of COPD hospitalizations in the last 12 months were collected at baseline using standardized methodology. The number of COPD hospitalizations (severe COPD exacerbations) and visits to the emergency room for

respiratory problems (as a surrogate for moderate exacerbations) during follow-up were obtained from the national administrative database. Both exacerbation history and exacerbations during follow-up were converted to binary variables (≥1 vs. 0).

Statistical analysis

Since the available sample size (n=114) was fixed by the primary objectives of the PAC-COPD study and availability of subjects with repeated measurements of the variables of interest, we calculated the statistical power to answer the current research question. Power calculations were performed for the decline in FEV_1, 6MWD, HGF, SGRQ and FFM and resulted in a range between 28% and 84%, using unpaired t-test ($p<0.05$) and assuming an equal number of active and inactive patients. The latter assumption has been confirmed as 54 patients (53%) were classified as inactive or very inactive at baseline (14).

We decided *a priori* to perform multiple imputation of the study completers (n=114) through chain equations in the case missing data could be considered as 'completely at random' or 'at random'. Missing values were imputed from predictive distributions of each variable, obtained from regression models where all the variables associated with the probability of missing and those associated with the outcomes were used as covariates. To account for the additional uncertainty produced by the fact that missing values are substituted by estimates, missing values were imputed 20 times. Supplementary Table 2 shows patients characteristics of the complete case and the imputed population.

Data are presented as mean (SD) or median [25^{th}-75^{th} percentile]; categorical variables are presented as n (%). *First*, we tested the association between each exposure variable (i.e., step count, MVPA, sedentary time) and each outcome variable (i.e., parameters of decline), adjusted for the baseline values of the corresponding outcome (proc GLM). The latter

decision takes into account the fact that, for each outcome, patients with high baseline values may have higher decline than those with low initial values. For this analysis, in order to help interpretation, exposure variables were classified in four groups. Based on the step count patients were classified as very inactive (<5000 steps.day^{-1}), inactive (5000-7500 steps.day^{-1}), somewhat active (7500-10000 steps.day^{-1}) and active (≥10000 steps.day^{-1}) (14). Time in MVPA and sedentary time were categorized in quartiles. *Second*, for each combination of exposure/outcome where bivariate analysis had suggested an association ($p<0.20$), multivariable models adjusted for baseline levels and confounders were built. Based on the normal distribution of outcomes and the shape of the relationship, analyzed using generalized additive models (proc GAM), we tested the associations using general linear models (proc GLM) with the exposure variables as continuous. We considered as potential covariables age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), participation in pulmonary rehabilitation, diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history (≥1 vs. 0), FEV_1 (% of the predicted value), hand grip force, 6MWD and duration of daylight. These variables were tested and included in the multivariable final models if (1) they were related to both the outcome and the exposure, (2) they changed the estimates of the multivariable model (>10%) or (3) the variable was consistently associated with COPD progression in literature. For all models goodness of fit was analyzed by means of heteroscedasticity and normality of the residuals.

We performed the following additional analyses: (i) to study the possible interaction between smoking status and PA on their effect on the disease progression, final step count models were stratified by baseline smoking status (current active smoker or not); (ii) to study possible interaction between PA and sedentary time on their effect on disease progression, we

stratified final sedentary time models for PA using the median of MVPA as threshold (52 min.day^{-1}); (iii) to test whether the association between PA and disease progression was mediated by an effect of PA on exacerbations, we additionally included the variable "COPD exacerbations during follow-up" (severe and/or moderate) in the final step count model; and (iv) to compare our results with the previous paper mentioned in the introduction (15) we divided patients into persistently inactive (step count <5000 steps.day^{-1} at baseline and follow-up), persistently active (step count ≥5000 steps.day^{-1} at baseline and follow-up) and activity decliners (step count ≥5000 steps.day^{-1} at baseline and <5000 at follow-up). One patient going from an inactive to an active status was excluded for these analyses. We compared disease progression between these 3 three groups by repeating the bivariate analyses, adjusted for the baseline values of the corresponding outcome.

Finally, we performed sensitivity analyses to assess the robustness of results: (i) excluding subjects with extreme values (<5th or >95th percentile) in the accelerometer measurements to discard observed associations driven by extreme values, (ii) repeating the multivariable models by using linear mixed models (proc mixed) to test for possible model misspecification, and (iii) excluding patients who were participating in a pulmonary rehabilitation program.

Multiple imputations were performed using STATA 12.1 (StataCorp, College Station, TX, USA) and statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Results based on the 20 imputed databases were combined using proc mianalyze. Statistical significance was set at $p<0.05$ for all the analyses.

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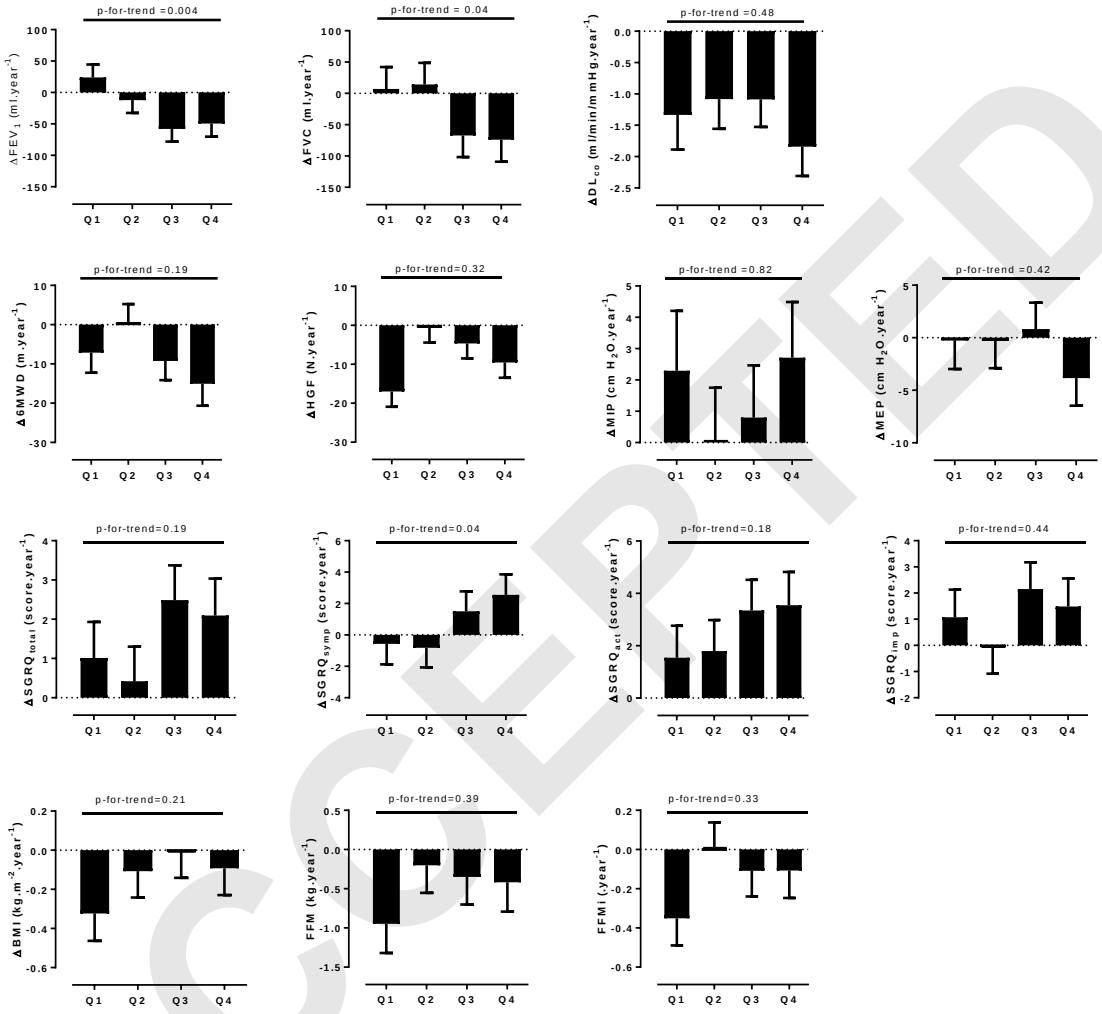
Supplementary Figure 1: Patients' annual change* in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline moderate-to-vigorous physical activity (MVPA) levels (quartiles).

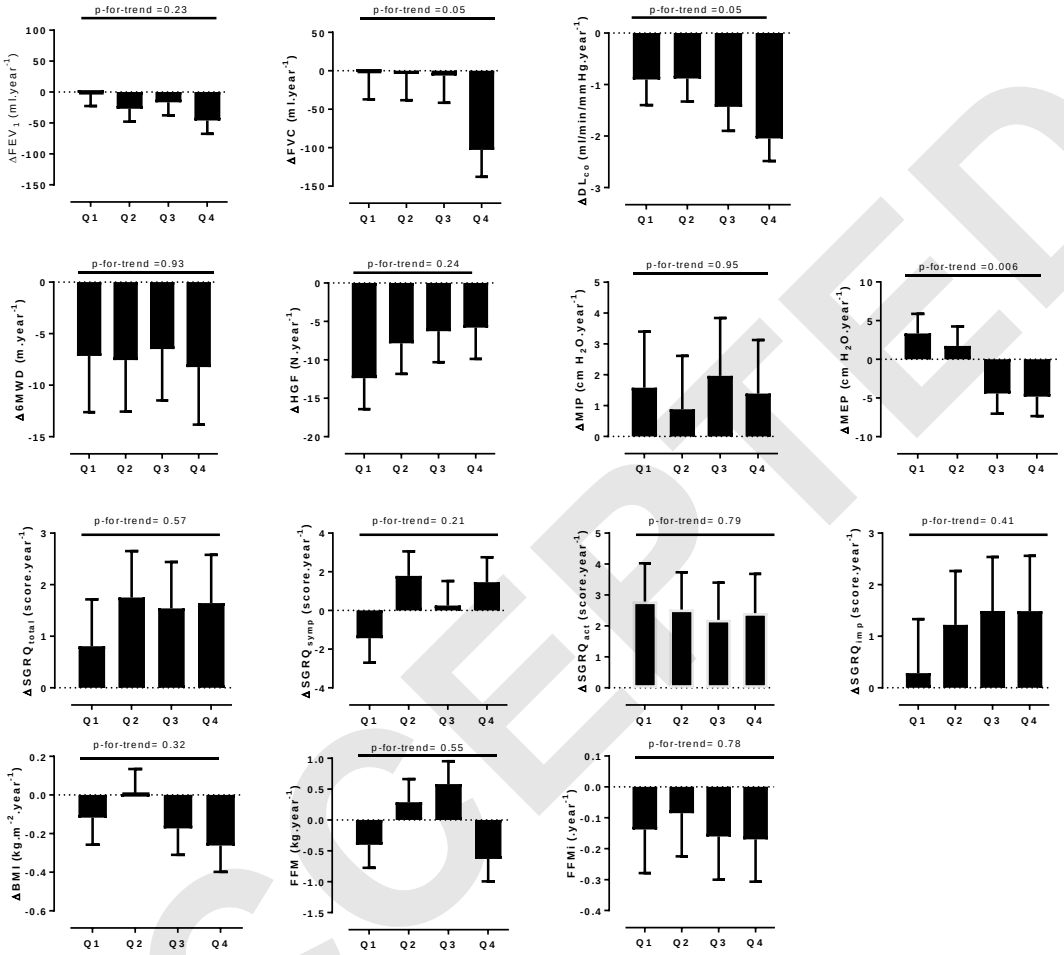


MVPA = moderate-to-vigorous physical activity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{CO} = diffusion capacity of the lung carbon monoxide, 6MWD = 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi= fat free mass index.

* Negative values represent a decline in the outcome measure.

Data presented as estimated marginal means (Least squares means) and SEM, adjusted for the baseline of the outcome of interest. Patients were divided in quartiles based on the mean time in moderate-to-vigorous physical activity (MVPA), from more MVPA (Q1) to less MVPA (Q4). P-values indicate p-for-trend.

Supplementary Figure 2: Patients' annual change* in outcomes of COPD progression during a mean follow-up of 2.6 years in 114 COPD patients, according to baseline sedentary time levels (quartiles).

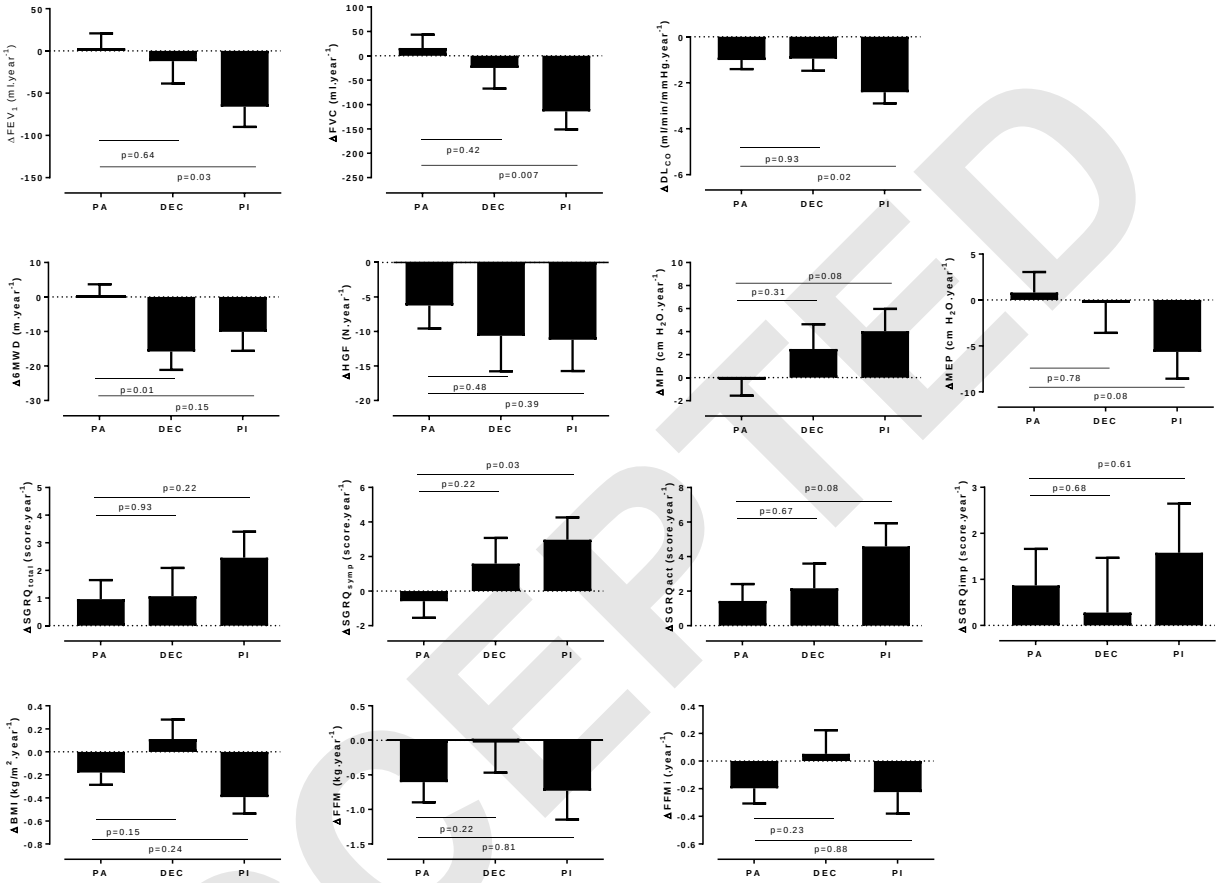


FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{CO} = diffusion capacity of the lung carbon monoxide, 6MWD = 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi= fat free mass index.

* Negative values represent a decline in the outcome measure.

Data presented as estimated marginal means (Least squares means), adjusted for the baseline of the outcome of interest. Patients were divided in quartiles based on the mean baseline sedentary time, from less sedentary (Q1) to more sedentary (Q4). P-values indicate p-for-trend.

Supplementary Figure 3: Patients' yearly changes in outcomes of COPD progression during a mean follow-up of 2.6 years , according to physical activity changes status (persistently active, decliners and persistently inactive).



FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{CO} = diffusion capacity of the lung carbon monoxide, 6MWD = 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi= fat free mass index.

Data presented as estimated marginal means (Least squares means), adjusted for the baseline of the outcome of interest. A subgroup of patients with PA data at both time points were divided into persistenly active (PA; mean step count ≥5000 steps.day^{-1} at both time points, n=47), decliners (DEC; mean step count ≥5000 steps.day^{-1} at baseline and <5000 steps.day^{-1} at follow-up, n=19) and persistently inactive (PI; mean step count <5000 steps.day^{-1} at baseline and follow-up, n=26). Solid lines represent the p-values compared to the PA group

Supplementary Table 1: Baseline characteristics of patients according to follow-up status.

	Patients followed (n=114)	Drop outs (n=63)		p-value*
		Lost to follow-up (n=36)	Deceased (n=27)	
Clinical data				
Age (years)	70 (8)	72 (9)	71 (6)	0.48
Sex: male	94%	94%	93%	0.96
Smoking status: active	30%	39%	33%	0.36
Charlson index≥2	55%	53%	63%	0.81
Work status Working	7%	11%	11%	0.40
Social status Non-manual work Manual work	18% 82%	28% 72%	16% 84%	0.47
Marital status Single Married or living together Widow Separated or divorced	7% 82% 7% 4%	6% 83% 11% 0%	4% 81% 11% 4%	0.64
Participation in PR	4%	8%	4%	0.65
≥1 COPD admission in the previous 12 months	11%	17%	22%	0.16
Lung function				
Spirometric severity (ATS/ERS I/II/III/IV)	6%/59%/27%/8%	6%/31%/58%/6%	0%/33%/44%/22%	0.01

FEV_1 (ml)	1620 (525)	1436 (504)	1283 (473) †	<0.01
FEV_1 (% predicted)	54 (16)	50 (15)	44 (15) †	<0.01
FVC (ml)	2942 (651)	2803 (838)	2635 (673) †	0.05
FVC (% predicted)	72 (15)	71 (19)	65 (13) †	0.11
DL_{co} (ml/min/mmHg)	16.5 (5)	15.1 (5)	12.9 (5)†	0.01
DL_{co} (% predicted)	66 (21)	63 (21)	52 (19) †	0.02
Exercise capacity and muscle force				
6MWD (m)	415 (95)	411 (96)	366 (94)	0.16
HGF (N)	295 (87)	265 (98)	275 (78)	0.07
MIP (cm H_2O)	-74 (26)	-64 (24)	-62 (20)	0.01
MEP(cm H_2O)	109 (36)	112 (42)	108 (25)	0.80
Symptoms and quality of life				
mMRC (0/1/2/3/4)	21/35/23/6/15	22/33/22/6/17	7/33/22/7/30	0.76
SGRQ total score (points)	29 (17)	34 (20)	41 (19)	<0.01
SGRQ symptoms (points)	26 (19)	34 (22)	35 (21)	0.01
SGRQ activity (points)	42 (24)	46 (26)	57 (26)	0.01
SGRQ impacts (points)	22 (16)	26 (20)	33 (20)	0.01
Body composition				
BMI ($kg.m^{-2}$)	29 (5)	28 (4)	27 (4)	<0.01
FFM (kg)	55 (10)	51 (9)	51 (8)	0.02
FFMi ($kg.m^{-2}$)	20 (3)	19 (3)	19 (2)	0.01
Physical activity and sedentary time				
Step count ($n.day^{-1}$)	7362 (4589)	6899 (4016)	5441 (6066)	0.15
MVPA ($min.day^{-1}$)	92 [22-91]	63 [18-96]	25 [9 – 117]	0.38
Sedentary time ($min.day^{-1}$)	624 (118)	628 (118)	676 (129)	0.20

PR= pulmonary rehabilitation, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, 6MWD= 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal

expiratory pressure, mMRC = modified Medical Research Council dyspnea scale, SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi = fat free mass index, MVPA = time in moderate-to-vigorous physical activity. Lung function results were expressed as a % of reference values of a Mediterranean population [E11, E12].

Data are presented as %, mean (SD) or median [25^{th}-75^{th} percentile]

* p-value indicates comparison between patients followed up (n=114) and those who dropped out (n=63)

† p-value comparing lost to follow-up *vs* deceased <0.05

Supplementary Table 2: Baseline characteristics of patients using complete cases and imputed data set.

	Missing data (n)	Complete cases	Multiple imputation
	N=114		
Clinical data			
Age (years)	0	70 (8)	70 (8)
Sex: male	0	94%	94%
Smoking status: active	0	30%	30%
Charlson index≥2	0	55%	55%
Work status Working	6	 7%	 9%
Social status Non-manual work Manual work	9	 18% 82%	 19% 81%
Marital status Single Married or living together Widow Separated or divorced	0	 7% 82% 7% 4%	 7% 82% 7% 4%
Participation in pulmonary rehabilitation	0	4%	4%
≥1 COPD admission in the previous 12 months	0	11%	11%
Lung function			
Spirometric severity (ATS/ERS I/II/III/IV)	0	6%/59%/27%/8%	6%/59%/27%/8%

FEV_1 (ml)	0	1620 (525)	1620 (525)
FEV_1 (% predicted)	0	54 (16)	54 (16)
FVC (ml)	0	2942 (651)	2942 (651)
FVC (% predicted)	0	72 (15)	72 (15)
DL_{co} (ml/min/mmHg)	14	17 (5)	16 (6)
DL_{co} (% predicted)	14	66 (21)	66 (24)
Exercise capacity and muscle force			
6MWD (m)	5	415 (95)	411 (98)
HGF (N)	0	295 (87)	295 (87)
MIP (cm H_2O)	17	-74 (26)	-73 (28)
MEP (cm H_2O)	17	109 (36)	106 (38)
Symptoms and quality of life			
mMRC (0/1/2/3/4)	0	21/35/23/6/15	21/35/23/6/15
SGRQ total score (points)	0	29 (17)	29 (17)
SGRQ symptoms (points)	0	26 (19)	26 (19)
SGRQ activity (points)	0	42 (24)	42 (24)
SGRQ impacts (points)	0	22 (16)	22 (16)
Body composition			
BMI ($kg.m^{-2}$)	0	29 (5)	29 (5)
FFM (kg)	7	55 (10)	55 (10)
FFMi ($kg.m^{-2}$)	7	20 (3)	20 (3)
Physical activity and sedentary time			
Step count ($n.day^{-1}$)	0	7362 (4589)	7362 (4589)
MVPA ($min.day^{-1}$)	0	52 [22-91]	52 [22-91]
Sedentary time ($min.day^{-1}$)	0	624 (118)	624 (118)
Annual change in outcomes of COPD progression			
FEV_1 ($ml.year^{-1}$)	0	-24.2 (112)	-24.2 (112)

FVC (ml.year^{-1})	0	-30.2 (189)	-30.2 (189)
DL_{co} (ml/min/mmHg.year^{-1})	32	-1.20 (1.92)	-1.33 (3)
6MWD (m.year^{-1})	15	-8.0 (23)	-7.7 (27)
HGF (N.year^{-1})	0	-7.8 (23)	-7.8 (23)
MIP (cm H_2O.year^{-1})	21	0.82 (8.8)	1.44 (10)
MEP (cm H_2O.year^{-1})	22	-1.19 (13)	-0.87 (15)
SGRQ total score (points.year^{-1})	2	1.50 (5.0)	1.33 (5)
SGRQ symptoms (points.year^{-1})	2	0.66 (7.4)	0.58 (8)
SGRQ activity (points.year^{-1})	2	2.56 (6.8)	2.30 (7)
SGRQ impacts (points.year^{-1})	2	1.16 (5.8)	1.00 (6)
BMI (kg.m^{-2}.year^{-1})	0	-0.13 (0.72)	-0.13 (0.72)
FFM (kg.year^{-1})	10	-0.40 (1.8)	-0.48 (2)
FFMi (kg.m^{-2}.year^{-1})	10	-0.11 (0.7)	-0.14 (0.8)

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, 6MWD= 6-min walk distance, HGF = hand grip force, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, mMRC = modified Medical Research Council dyspnea scale, SGRQ = Saint George's respiratory questionnaire, BMI = body mass index, FFM = fat free mass, FFMi = fat free mass index, MVPA = time in moderate-to-vigorous physical activity. Lung function results were expressed as a % of reference values of a Mediterranean population (Roca, 1986 and Roca, 1990).

Data are presented as %, mean (SD) or median [25^{th}-75^{th} percentile]

Supplementary Table 3: Average annual change* in exercise capacity, respiratory muscle force and other domains of health status related to baseline step count (multivariable linear regression model†).

	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value
Δ6MWD (m.year^{-1})	0.94 (-0.29 to 2.17)	0.13
ΔMIP (cm H_2O.year^{-1})	-0.14 (-0.21 to -0.06)	0.30
ΔMEP (cm H_2O.year^{-1})	0.29 (-0.31 to 0.90)	0.35
$\Delta SGRQ_{total}$score (points.year^{-1})	-0.16 (-0.39 to 0.07)	0.17
$\Delta SGRQ_{activity}$score (points.year^{-1})	-0.13 (-0.43 to 0.18)	0.42
$\Delta SGRQ_{impacts}$score (points.year^{-1})	-0.14 (-0.41 to 0.13)	0.31

6MWD = 6-min walk distance, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure, SGRQ = Saint George's respiratory questionnaire.

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for baseline value of the corresponding outcome and (i) age, sex, exacerbation history (≥1 / 0), Fat free mass, FEV_1% predicted and duration of daylight for 6MWD, (ii) age, sex, exacerbation history, Fat free mass, FEV_1% predicted, 6MWD and duration of daylight for respiratory muscle force or (iii) age, sex, exacerbation history (≥1 / 0), smoking status (current / not current), FEV_1% predicted, 6MWD and duration of daylight for SGRQ. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the methods (complete version).

Supplementary Table 4: Average annual change* in lung function and symptoms domain of health status related to baseline sedentary time (multivariable linear regression model†), according to baseline moderate-to-vigorous physical activity (MVPA).

	Low MVPA (<52 min.day^{-1})	High MVPA (≥ 52 min.day^{-1})	
	Per hour.day^{-1} increase in sedentary time Estimate (95% CI)	Per hour.day^{-1} increase in sedentary time Estimate (95% CI)	p-value
ΔFEV_1 (ml.year^{-1})	-5.90 (-27 to 15)	-6.77 (-28 to 14)	0.95
ΔFVC (ml.year^{-1})	-23.22 (-63 to 17)	-0.87 (-30 to 28)	0.39
ΔDL_{co} (ml/min/mmHg.year^{-1})	-0.43 (-0.82 to -0.05)	-0.29 (-0.68 to 0.10)	0.97
$\Delta SGRQ_{symptoms}$score (points.year^{-1})	0.71 (-0.67 to 2.08)	0.20 (-0.80 to 1.20)	0.32

MVPA = moderate-to-vigorous physical activity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, SGRQ = Saint George's respiratory questionnaire.

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for baseline value of the corresponding outcome and (i) age, sex, exacerbation history (≥1 / 0), BMI, Charlson index, smoking status (current / not current), pack-years and duration of daylight for lung function variables, or (ii) age, sex, exacerbation history (≥1 / 0), smoking status, FEV_1% predicted, 6MWD and duration of daylight for SGRQ. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the methods (complete version).

Supplementary Table 5: Average annual change* in lung function and symptoms domain of health status related to baseline step count (multivariable linear regression model†), with and without having exacerbations during follow-up as a covariate.

	Without exacerbations during follow-up in the model		Including exacerbations during follow-up (≥1 vs. 0) in the model	
	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value
ΔFEV_1 (ml.year^{-1})	7.26 (2.3 to 12.2)	0.005	7.41 (2.3 to 12.5)	0.005
ΔFVC (ml.year^{-1})	8.78 (0.7 to 16.9)	0.034	8.91 (0.6 to 17.2)	0.036
ΔDL_{co} (ml/min/mmHg.year^{-1})	0.10 (0.0 to 0.2)	0.036	0.09 (0.0 to 0.1)	0.055
$\Delta SGRQ_{symptoms}$score (points.year^{-1})	-0.36 (-0.7 to 0.0)	0.027	-0.35 (-0.7 to 0.0)	0.023

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, SGRQ = Saint George's respiratory questionnaire.

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for baseline value of the corresponding outcome and (i) age, sex, exacerbation history (≥1 / 0), BMI, Charlson index, smoking status (current / not current), pack-years and duration of daylight for lung function variables, or (ii) age, sex, exacerbation history (≥1 / 0), smoking status, FEV_1% predicted, 6MWD and duration of daylight for SGRQ. Having a COPD exacerbation during follow-up was included as a binary variable in the models. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the methods (complete version).

Supplementary Table 6: Average annual change* in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable linear regression model†) after excluding extreme values of physical activity variables.

	Step count		MVPA		Sedentary time	
	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value	Per 10 minutes.day^{-1} increase Estimate (95% CI)	p-value	Per hour.day^{-1} increase Estimate (95% CI)	p-value
ΔFEV_1 (ml.year^{-1})	8.3 (1.2 to 15.3)	0.02	6.49 (1.0 to 12.0)	0.02	-2.93 (-18.6 to 12.7)	0.71
ΔFVC (ml.year^{-1})	13.3 (2.2 to 24.3)	0.02	6.98 (-2.0 to 15.9)	0.12	-17.94 (-45.6 to 9.7)	0.20
ΔDL_{co} (ml/min/mmHg.year^{-1})	0.17 (0.04 to 0.30)	0.01	0.03 (-0.08 to 0.15)	0.58	-0.28 (-0.59 to 0.03)	0.08
$\Delta SGRQ_{symptoms}$score (points.year^{-1})	-0.47 (-0.90 to -0.03)	0.03	-0.29 (-0.64 to 0.05)	0.10	0.37 (-0.53 to 1.27)	0.42

MVPA = moderate-to-vigorous physical activity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, SGRQ = Saint George's respiratory questionnaire. Analyses are bases on 103 patients (step count and MVPA) or 102 patients (sedentary time).

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for baseline value of the corresponding outcome and (i) age, sex, exacerbation history (≥1 / 0), BMI, Charlson index, smoking status (current / not current), pack-years and duration of daylight for lung function variables, or (ii) age, sex, exacerbation history (≥1 / 0), smoking status, FEV_1% predicted, 6MWD and duration of daylight for SGRQ. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the methods (complete version).

Supplementary Table 7: Average annual change* in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable mixed model†).

	Step count		MVPA		Sedentary time	
	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value	Per 10 minutes.day^{-1} increase Estimate (95% CI)	p-value	Per hour.day^{-1} increase Estimate (95% CI)	p-value
ΔFEV_1 (ml.year^{-1})	4.69 (0.3 to 9.1)	0.037	4.85 (1.56 to 8.14)	0.004	-8.81 (-19 to 1.5)	0.09
ΔFVC (ml.year^{-1})	5.12 (-1.8 to 12.1)	0.15	3.14 (-2.15 to 8.44)	0.24	-12.42 (-28.5 to 3.7)	0.13
ΔDL_{co} (ml/min/mmHg.year^{-1})	0.07 (-0.03 to 0.17)	0.17	-0.01 (-0.09 to 0.07)	0.74	-0.10 (-0.35 to 0.15)	0.41
$\Delta SGRQ_{symptoms}$score (points.year^{-1})	-0.23 (-0.52 to 0.07)	0.12	-0.24 (-0.46 to -0.02)	0.04	0.68 (0.01 to 1.35)	0.05

MVPA= moderate-to-vigorous physical activity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, SGRQ = Saint George's respiratory questionnaire.

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for (i) age, sex, exacerbation history (≥1 / 0), BMI, Charlson index, smoking status (current / not current), pack-years and duration of daylight for lung function variables, or (ii) age, sex, exacerbation history (≥1 / 0), smoking status, FEV_1% predicted, 6MWD and duration of daylight for SGRQ. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the methods (complete version)

Supplementary Table 8: Average annual change* in lung function and symptoms domain of health status related to step count, sedentary time and moderate-to-vigorous physical activity (MVPA) at baseline (multivariable linear regression model) after excluding patients participating in a pulmonary rehabilitation program at baseline (n=4)

	Step count		MVPA		Sedentary time	
	Per 1000 increase in steps.day^{-1} Estimate (95% CI)	p-value	Per 10 minutes.day^{-1} increase Estimate (95% CI)	p-value	Per hour.day^{-1} increase Estimate (95% CI)	p-value
ΔFEV_1 (ml.year^{-1})	7.00 (2.2 to 11.8)	<0.01	5.13 (1.53 to 8.28)	<0.01	-14 (-25 to -2.4)	0.02
ΔFVC (ml.year^{-1})	8.48 (0.29 to 16.7)	0.04	4.99 (-1.35 to 11.33)	0.12	-21 (-42 to -0.4)	0.046
ΔDL_{co} (ml/min/mmHg.year^{-1})	0.10 (0.06 to 0.14)	0.04	0.03 (-0.05 to 0.10)	0.49	-0.25 (-0.5 to 0.01)	0.06
$\Delta SGRQ_{symptoms}$score (points.year^{-1})	-0.35 (-0.67 to -0.02)	0.03	-0.20 (-0.45 to 0.05)	0.12	0.81 (0.0 to 1.6)	0.04

MVPA = moderate-to-vigorous physical activity, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, DL_{co} = diffusion capacity of the lung carbon monoxide, SGRQ = Saint George's respiratory questionnaire. Analyses are bases on 109 patients (step count and MVPA) or 108 patients (sedentary time).

* Negative values represent a decline in the outcome measure.

† Every cell is a single multivariable model adjusted for baseline value of the corresponding outcome and (i) age, sex, exacerbation history (≥1 / 0), BMI, Charlson index, smoking status (current / not current), pack-years and duration of daylight for lung function variables, or (ii) age, sex, exacerbation history (≥1 / 0), smoking status, FEV_1% predicted, 6MWD and duration of daylight for SGRQ. The full list of potential confounders included: age, sex, education, marital status, work status, baseline smoking status, smoking history expressed as pack-years, medication (including long acting bronchodilators, inhaled corticosteroids and a combined inhaled therapy), diet (including vegetables, meat and fruit intake), Charlson index, BMI, FFM, FFMi, mMRC, COPD exacerbation history, FEV_1 % predicted, hand grip force, 6MWD and duration of daylight. Criteria for keeping them in the final model are detailed in the methods (complete version)