Physical Activity Is Associated with Attenuated Disease Progression in Chronic Obstructive Pulmonary Disease

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ABSTRACT

DEMEYER, H., D. DONAIRE-GONZALEZ, E. GIMENO-SANTOS, M. A. RAMON, J. DE BATTLE, M. BENET, I. SERRA, S. GUERRA, E. FARRERO, E. RODRIGUEZ, J. FERRER, J. SAULEDA, E. MONSO, J. GEA, R. RODRIGUEZ-ROISIN, A. AGUSTI, J. M. ANTÓ, and J. GARCIA-AYMERICH. Physical Activity Is Associated with Attenuated Disease Progression in Chronic Obstructive Pulmonary Disease. *Med. Sci. Sports Exerc.*, Vol. 51, No. 5, pp. 833–840, 2019. **Introduction**: Chronic obstructive pulmonary disease (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. **Methods**: We studied 114 COPD patients from the PAC-COPD cohort (94% male, mean [SD], 70 yr [8 yr] of age, 54 [16] forced expiratory volume in 1 s % predicted) at baseline and 2.6 yr (0.6 yr) 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, forced expiratory volume in 1 s declined 7 mL less ($P < 0.01$), forced vital capacity 9 mL less ($P = 0.03$) and carbon monoxide diffusing capacity 0.10 mL·min^{-1}·mm Hg^{-1} less ($P = 0.04$), while the St George's Respiratory Questionnaire symptom domain deteriorated 0.4 points less ($P = 0.03$), per year follow-up. Physical activity was not associated with changes in functional exercise capacity, muscle strength, other domains of health status or body composition. **Conclusions**: 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

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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 because 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 multidimensional 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, dyspnea 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), behavioral 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 meager, 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-yr decline in functional exercise capacity and in fat-free mass (FFM) (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 FFM 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 yr (0.6 yr) (follow-up visit of the present article) 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, Supplemental Digital Content 2, Baseline characteristics 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. Physical activity was measured by the Sensewear PRO armband (Body Media, Pittsburgh, PA), previously validated in COPD patients (18), at baseline and during follow-up. Patients were asked to wear the monitor during seven consecutive days. Waking hours (from 8:00 AM to 10:00 PM) were selected and a valid measurement was defined *a priori* as at having at least 3 d 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) postbronchodilator forced spirometry (forced expiratory volume in 1 s [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 (HGF) of the nondominant hand and maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP); 4) health status by the Saint George's Respiratory Questionnaire (SGRQ); and 5) body composition expressed as body mass index (BMI), 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), sociodemographic 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.

TABLE 1. Baseline characteristics of 114 COPD patients.

Sex: male	94%
Age (yr)	70 (8)
Smoking status: active	30%
FEV_1 (% predicted)	54 (16)
FVC (% predicted)	72 (15)
DL_{co} (% predicted)[a]	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[a]	9%
Charlson Index ≥2	55%
Long acting bronchodilator therapy[b]	85%
Inhaled corticosteroids therapy[c]	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 (steps·d^{-1})	7362 (4589)
MVPA (min·d^{-1})	52 [22–91]
Sedentary time (min·d^{-1})	624 (118)
Physically very inactive (<5000 steps per day)	37 (32)

Data are presented as %, mean (SD) or median [25th–75th percentile].
[a]Descriptive analyses conducted using imputed dataset in the case of missing data.
[b]Long acting muscarinic agents (LAMA) or long-acting beta agonists (LABA) alone or in combination with other inhaled medications.
[c]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).
mMRC, modified Medical Research Council dyspnea scale; ATS, American Thoracic Society.

Statistical analysis. Sample size calculations and treatment of missing data (multiple imputation through chain equations) are detailed in the supplement (see Appendix, Supplemental Digital Content 1, Methods, http://links.lww.com/MSS/B462). Supplementary Table 2 Supplemental Digital Content 3, shows patients characteristics of the complete case and the imputed population. Data are presented as mean (SD) or median [25th–75th 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 Appendix, Supplemental Digital Content 1, Methods 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 article by Waschki et al. (5). Finally, as sensitivity analyses, we 1) excluded subjects with extreme values in the accelerometer measurements, 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 per day. After 2.6 yr (0.6 yr) 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·yr^{-1}; 6MWD, -7.7 m·yr^{-1}; HGF, -7.8 N·yr^{-1}; total SGRQ, +1.44 points per year; and FFM, -0.48 kg·yr^{-1}; Table 2).

Relationship between PA and disease progression. Figures 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^{-1}·mm Hg^{-1} 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 Supplementary Table 3, Supplemental Digital Content 4, Change in exercise capacity, respiratory muscle force, and other domains of health status related to baseline step count, http://links.lww.com/MSS/B465). Bivariate associations were similar with MVPA (see Supplementary Figure 1, Supplemental Digital Content 5, COPD progression according to baseline MVPA levels, http://links.lww.com/MSS/B466) or sedentary time (see Supplementary Figure 2, Supplemental Digital Content 6, COPD progression according to baseline sedentary time levels according to baseline sedentary time levels, 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.

TABLE 2. COPD progression: Average annual changes during a mean follow-up of 2.6 yr.

	Baseline	Follow-up	Decline (per Year)
FEV_1 (mL)	1620 (525)	1550 (563)	−24.2 (112)*
FVC (mL)	2942 (651)	2849 (741)	−30.2 (189)
DL_{co} (mL·min^{-1}·mm Hg^{-1})[a]	16.4 (6)	13.0 (7)	−1.33 (3)*
6MWD (m)[a]	411 (98)	389 (117)	−7.7 (27)*
HGF (N)	295 (87)	272 (84)	−7.84 (23)*
MIP (cm H_2O)[a]	−73 (28)	−68 (27)	1.44 (10)
MEP (cm H_2O)[a]	106 (38)	105 (37)	−0.87 (15)
SGRQ total score (points)[a]	29 (17)	33 (18)	1.33 (5)*
SGRQ symptoms (points)[a]	26 (19)	28 (21)	0.58 (8)
SGRQ activity (points)[a]	42 (24)	48 (24)	2.30 (7)*
SGRQ impacts (points)[a]	22 (16)	25 (18)	1.00 (6)
BMI (kg·m^{-2})	29 (5)	29 (9)	−0.13 (0.72)
FFM (kg)[a]	55 (10)	54 (10)	−0.48 (1.9)*
FFMi (kg·m^{-2})[a]	19.9 (3)	19.6 (3)	−0.14 (0.8)

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

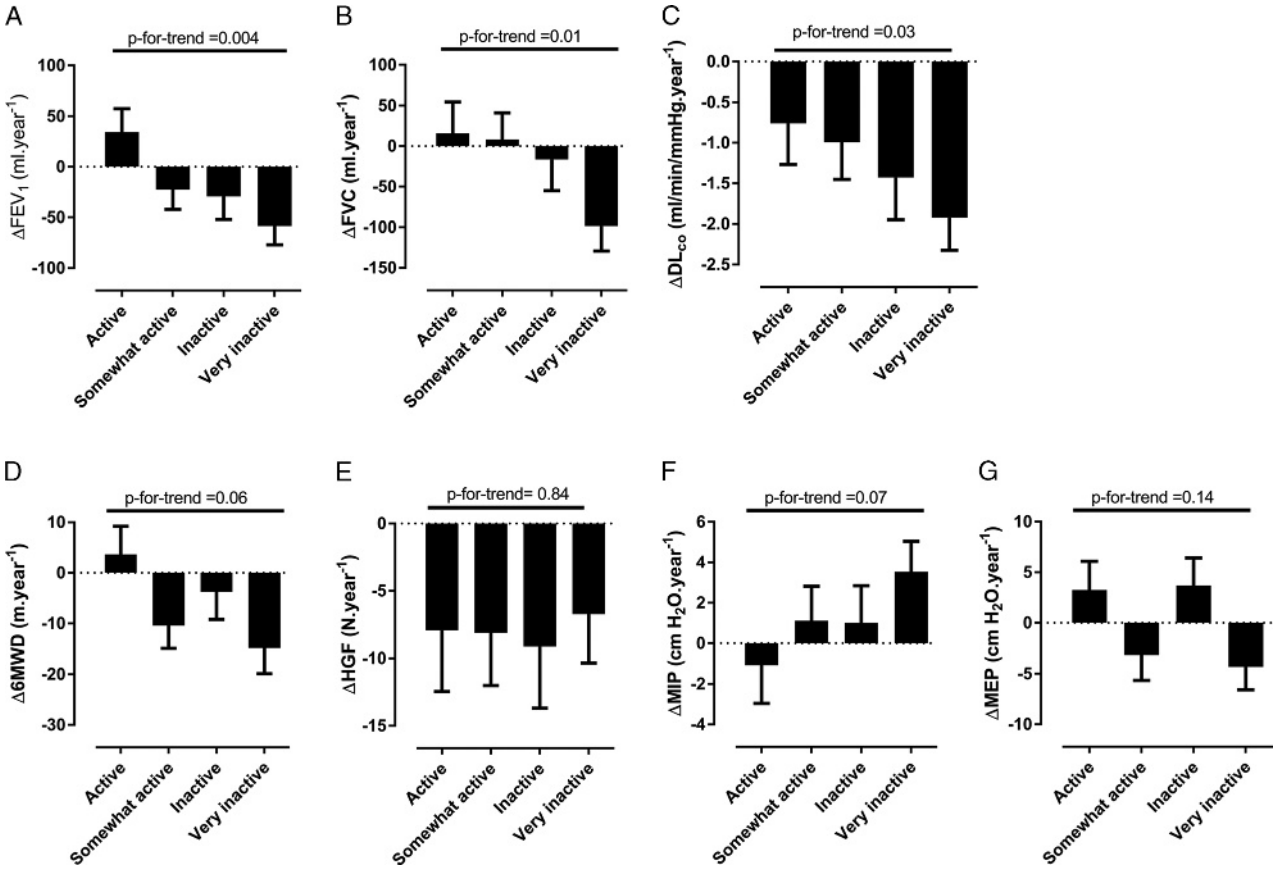

FIGURE 1—Patients' annual change in outcomes of COPD progression (lung function [panels A–C], functional exercise capacity [panel D] and muscle strength [panels E–G]) during a mean follow-up of 2.6 yr in 114 COPD patients, according to baseline physical activity (step count) levels. Negative values represent 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 four groups based on the mean baseline step count: Active (≥10,000 steps per day, *n* = 23), somewhat active (7500–10,000 steps per day, *n* = 31), inactive (5000–7500 steps per day, *n* = 23) and very inactive (<5000 steps per day, *n* = 37). *P* values indicate p-for-trend.

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 mL·yr^{-1} (4.2 mL·yr^{-1}) less (vs 4.6 mL·yr^{-1} [3.2 mL·yr^{-1}] 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 Supplementary Table 4, Supplemental Digital Content 7, change in lung function and symptoms domain of health status related to baseline sedentary time, according to baseline 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 Supplementary Table 5, Supplemental Digital Content 8, 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 per day ($P < 0.001$). When dividing these patients into persistently inactive, persistently active and PA decliners (see Supplementary Figure 3, Supplemental Digital Content 9, COPD progression according to physical activity changes status, 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:

- Supplementary Table 6, Supplemental Digital Content 10, Change in lung function and symptoms domain of health status related to step count, sedentary time and MVPA at baseline after excluding extreme values of physical activity variables, http://links.lww.com/MSS/B471
- Supplementary Table 7, Supplemental Digital Content 11, Change in lung function and symptoms domain of health status related to step count, sedentary time, and MVPA at baseline (multivariable mixed model), http://links.lww.com/MSS/B472
- Supplementary Table 8, Supplemental Digital Content 12, Change in lung function and symptoms domain of health status related to step count, sedentary time, and MVPA at

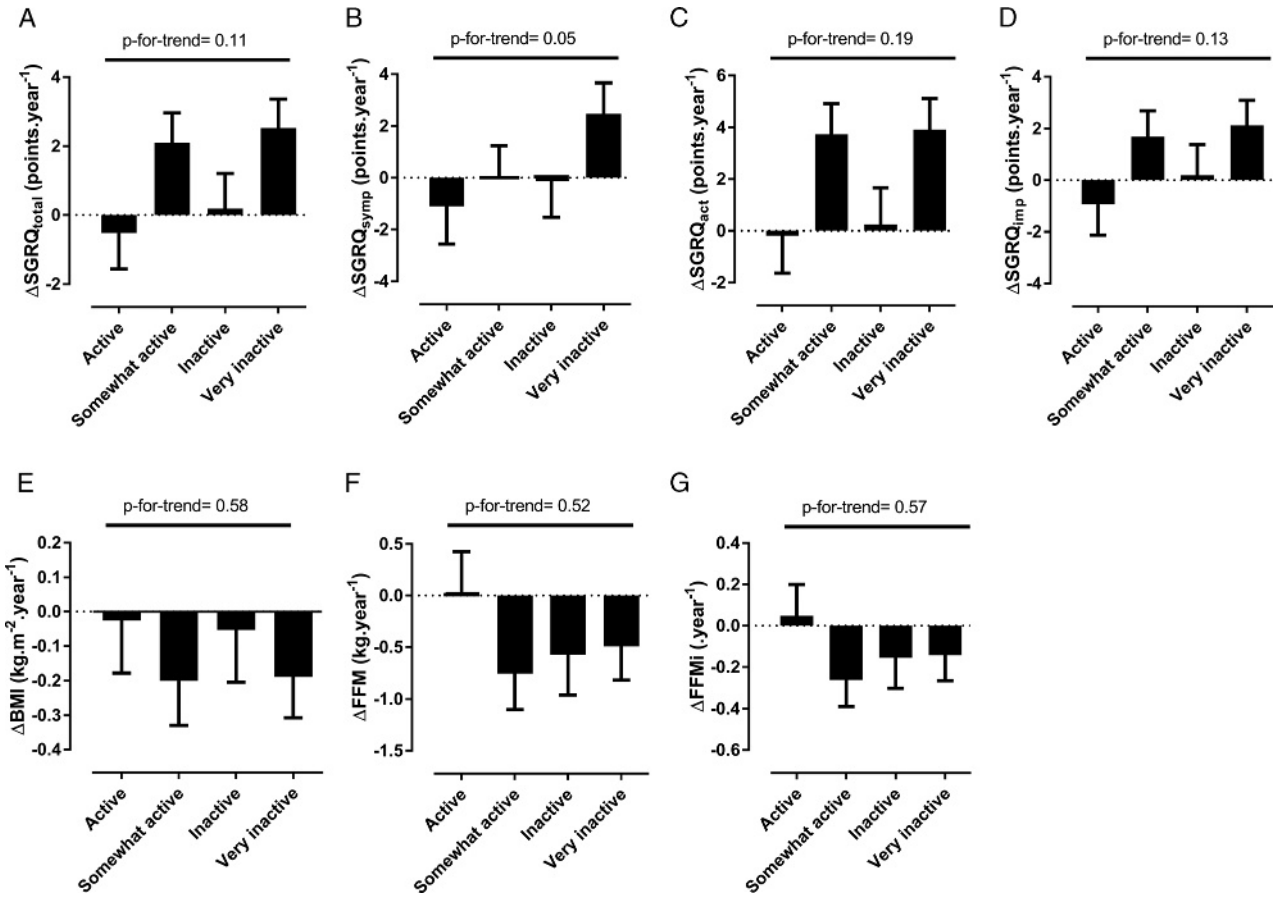

FIGURE 2—Patients' annual change in outcomes of COPD progression [health status (panel A–D) and body composition (panels E–G)] during a mean follow-up of 2.6 yr in 114 COPD patients, according to baseline physical activity (step count) levels. Negative values represent a decline in the outcome measure. Data presented as estimated marginal means (Least squares means) and SEM, adjusted for the baseline of the outcome of interest. Patients were divided into four groups based on the mean baseline step count: Active (≥10,000 steps per day, *n* = 23), somewhat active (7500–10,000 steps per day, *n* = 31), inactive (5000–7500 steps per day, *n* = 23) and very inactive (<5000 steps per day, *n* = 37). *P* values indicate p-for-trend.

baseline 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 to 3 yr 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). Because 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

TABLE 3. Average annual change[a] in lung function and symptoms domain of health status related to baseline step count, MVPA and sedentary time (multivariable linear regression model[b]).

	Step Count		MVPA		Sedentary Time	
	Per 1000 Steps per Day Increase, Estimate (95% CI)	*P*	Per 10 min·d^{-1} Increase Estimate (95% CI)	*P*	Per 1 h·d^{-1} Increase Estimate (95% CI)	*P*
ΔFEV_1 (mL·yr^{-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·yr^{-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^{-1}·mm Hg^{-1}·yr^{-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 per year)	−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

[a]Negative values represent a decline in the outcome measure.
[b]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 online supplement.

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 related to PA in (ex-) smokers with airflow obstruction (23).

Several, nonmutually exclusive, mechanisms can contribute to explain the observed association between PA and lung function decline: 1) PA can have an anti-inflammatory or antioxidant 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 Supplementary Table 5, Supplemental Digital Content 8, 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 Supplementary Table 3, Supplemental Digital Content 4, Change in exercise capacity, respiratory muscle force and other domains of health status related to baseline step count, 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), although 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 $mL \cdot yr^{-1}$ 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 induces 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 behavioral 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 nonsmokers (1). The attenuation seen for every 1000 steps of more physical activity can thus in magnitude be seen as one 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 behavior. 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). DL_{co} is an important 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). Physical activity 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 analyzing 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 Supplementary Table 1, Supplemental Digital Content 2, Baseline characteristics 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 yr 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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