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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