




Both moderate and severe exacerbations accelerate physical activity decline in COPD patients

To the Editor:

Physical activity (PA) is a relevant outcome measure in chronic obstructive pulmonary disease (COPD). Low PA is prevalent and drives prognosis [1]. Unfortunately, the determinants of PA and its change over time are poorly understood [1]. The fact that the PA progressively declines over time along with worsening of lung function and health status [2] suggests that the PA decline could be due to the progression of the disease and specifically to acute exacerbations [3]. An acute reduction in PA at the onset has been reported both in severe exacerbations requiring a hospitalisation [4] and in ambulatory treated exacerbations [5, 6]. A sustained PA reduction has been shown 1 month after hospital discharge [4] whereas PA almost returns to stable levels after community-treated exacerbations [6]. One study found faster PA decline in patients with a history of two or more exacerbations in the 12 months prior to the study [5]. This analysis did not adjust for confounders of the association (e.g. airflow obstruction, symptom burden) or external variables influencing PA (e.g. climate). It could also be argued that the greater decline in PA was due to lower health status at baseline. Although PA is an important outcome for COPD patients, little is known about the role of exacerbations in patients' experience of PA. Importantly, both the amount of activity and difficulties experienced during activity are integral to the concept of PA limitation [7]. The aim of the present analysis was to assess the association between the number and severity of exacerbations and changes in PA and PA experience.

As part of the IMI-JU PROactive study [7, 8], patients with COPD from mixed healthcare settings (tertiary hospitals, rehabilitation centres and primary care) in five European centres (Athens, Greece; Edinburgh and London, UK; Leuven, Belgium; and Groningen, The Netherlands) were studied at baseline and at 12 months' follow-up. Patients followed and those lost to follow-up were similar. Objective PA was measured using the Dynaport Movemonitor accelerometer (McRoberts BV, The Hague, The Netherlands). The main PA outcome analysed was the change (difference between baseline and 1 year) in daily step count; the secondary outcome was the change in intensity during locomotion. Patient experience of PA was assessed with the Clinical visit PROactive Physical Activity in COPD (C-PPAC) instrument [7], which consists of a total score and amount and difficulty scores. The number and severity of COPD exacerbations during the 12-month follow-up was retrieved [8]. We defined exacerbations as moderate (treated in an ambulatory setting with systemic antibiotics and/or systemic glucocorticosteroids) or severe (requiring hospital admission), following the GOLD initiative guidelines [9]. In addition to the number of exacerbations, we generated a variable combining the number and the severity of exacerbations. The association between exacerbation variables and PA change was analysed using regression analysis adjusted for baseline PA values. To remove the effect of potential confounders (listed in the caption of figure 1), we built a multivariable linear model for each PA outcome. Sensitivity analyses were performed excluding patients 1) with a COPD admission in the year before recruitment, 2) with extreme PA values (≤ 5 th or ≥ 95 th percentiles) and 3) with a COPD admission 2 months prior to the final measurement to exclude an acute effect. As *post hoc* explanatory analyses we tested the (bivariate) association between exacerbation variables and change in forced expiratory volume in 1 s (FEV₁), 6-min walk distance (6MWD) and modified Medical Research Council (mMRC) score, adjusted for baseline. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

The present analysis is based on 141 patients with valid data at baseline and follow-up (75% male, with a mean \pm SD age of 67 \pm 8 years, BMI 27 \pm 5 kg·m⁻², FEV₁ 59 \pm 21% predicted) of whom 81 (57%) experienced

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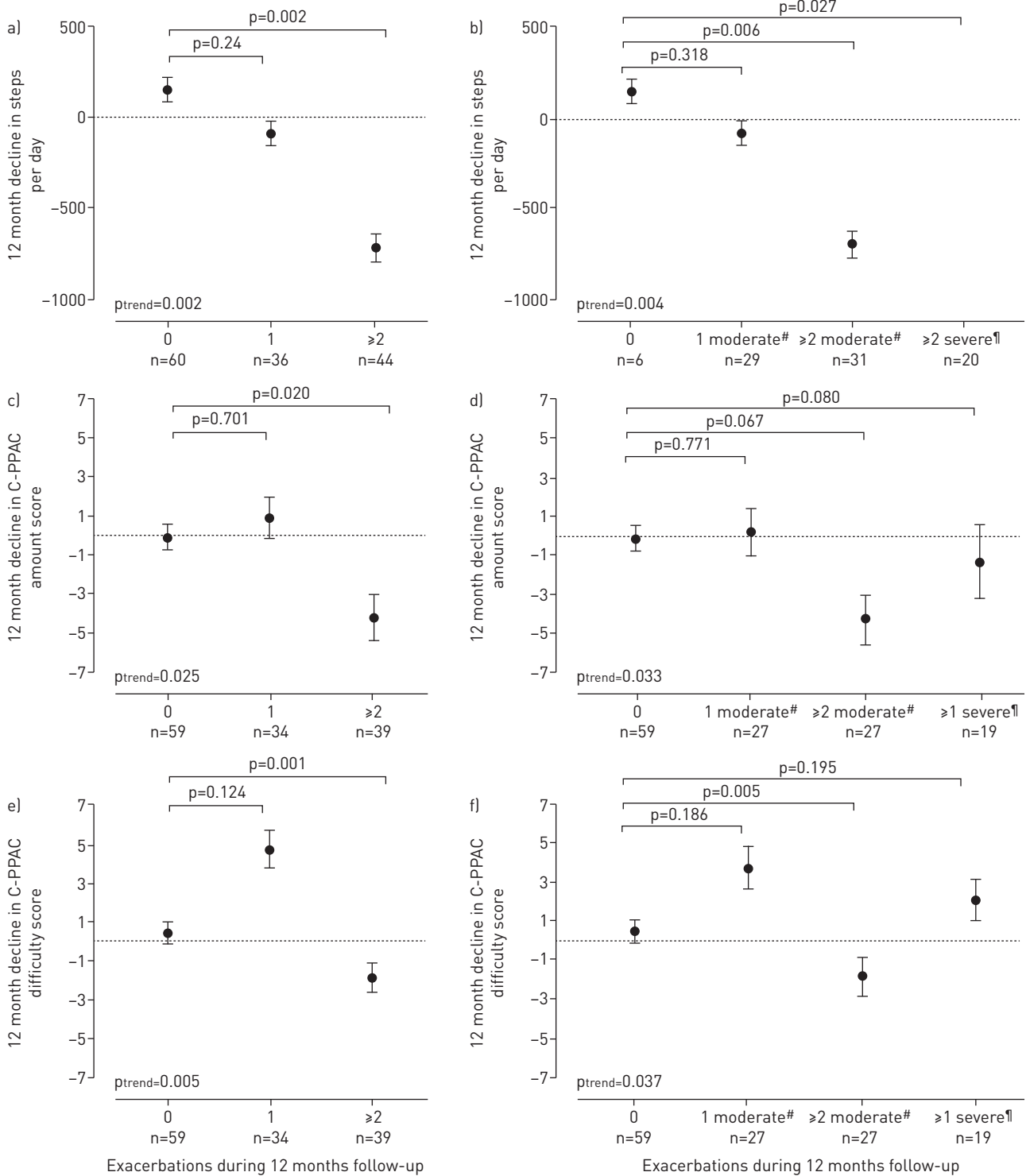


FIGURE 1 Decline in step count (a, b) and Clinical visit PROactive Physical Activity in COPD (C-PPAC) instrument score (c–f) according to chronic obstructive pulmonary disease (COPD) exacerbations in the 12-month follow-up (multivariable linear regression). Data are presented as estimated marginal means (least squares means) and SEM. Final models are adjusted for baseline physical activity and total COPD assessment test (CAT) score. Other potential confounders (age, gender, smoking habit, body mass index, any COPD admissions in previous 12 months, forced expiratory volume in 1 s (FEV₁) % predicted, forced vital capacity (FVC) % predicted, FEV₁/FVC ratio, American Thoracic Society/European Respiratory Society stage, 6-min walking distance, modified Medical Research Council score and Hospital Anxiety and Depression Scale scores) were tested and finally not included because they were not independently related to both the exposure and the outcome, nor modified (>10% change) the estimates for the remaining variables. #: patients without severe exacerbations; ¶: irrespective of the number of moderate exacerbations.

at least one exacerbation during follow-up. In the whole group there was a small, nonsignificant decline in step count (5209±3050 steps per day at baseline *versus* 5019±3099 steps per day at follow-up), while movement intensity (1.82±0.26 m·s⁻² at baseline *versus* 1.80±0.28 m·s⁻² at follow-up), exercise capacity (452±119 m at baseline *versus* 450±123 m at follow-up) and FEV₁ (1.62±0.69 L at baseline *versus* 1.63±0.69 L at follow-up) did not change. Patients had a baseline mean C-PPAC total score of 69±13, with domain scores for amount and difficulty 64±16 and 74±15, respectively.

The number of exacerbations was related to the decline in step count. In the multivariable model, a mean±SE change of 251±207, -144±262 and -797±244 steps per day was observed in patients who had presented no, one, or two or more exacerbations during follow-up respectively (figure 1a). Patients experiencing two or more moderate exacerbations (-753 steps per day) and those experiencing at least one severe exacerbation (-705 steps per day) showed a larger decline in PA than those with no exacerbations (figure 1b). There was no association between exacerbations during follow-up and changes in PA intensity (m·s⁻²). In relation to patient experience of PA, figure 1c and e show that patients with two or more exacerbations suffered more deterioration in C-PPAC amount (-4.2 points) and difficulty (-1.9 points) scores than patients having no or only one exacerbation. Patients experiencing two or more moderate exacerbations or at least one severe exacerbation showed a larger decline in C-PPAC amount and difficulty scores than those with no exacerbations; however, some of these associations were not statistically significant (figure 1d and f). All sensitivity analyses yielded similar results. Having exacerbations was related to a significant (p<0.01) larger increase in mMRC score but not to changes in 6MWD or FEV₁.

The present analyses show that the acute drop in PA after an exacerbation [4-6] has an important and lasting effect that cannot be attributed to confounders or baseline PA. A higher exacerbation frequency was, as expected, associated with a more pronounced PA decline. Patients with frequent exacerbations constitute a specific disease phenotype with a worse prognosis, specifically a faster loss in lung function [10], a greater worsening of health status [11] and a substantial reduction in the amount of PA (-797 steps per day) as indicated by our findings. An unexpected finding from this study is that two or more moderate events result in a long-term decline that is clinically relevant [12] and equivalent to that of a severe event, confirming the importance of prevention and early management of exacerbations regardless of the severity [9].

The fact that exacerbations result in a decrease in the amount of PA can be interpreted as part of the multiple systemic consequences [9]. First, we could hypothesise that the decline is a consequence of a loss in exercise capacity. Against this hypothesis, our data fail to show an association between exacerbations during follow-up and changes in exercise capacity. Second, the PA decline could potentially be explained based on a worsening of symptoms during an exacerbation leading to more inactivity, bringing patients in a vicious cycle of symptoms and inactivity [13]. Based on our explanatory analysis showing an association between exacerbations and an increase in dyspnoea, the latter hypothesis would be a plausible mechanism.

The present results have important implications for daily clinical practice and underscore the importance of identifying frequent exacerbators, as supported by the combined GOLD classification [9]. Our results support the promotion of interventions to increase PA, such as coaching programmes in the less [14] or pulmonary rehabilitation in the more severe patients [15] after an exacerbation.

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