



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

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| Complete List of Authors:     | <p>Demeyer, Heleen; KU Leuven, Department of Rehabilitation Sciences; ISGlobal, Centre for Research in Environmental Epidemiology (CREAL); Universitat Pompeu Fabra (UPF), CIBER Epidemiología y Salud Pública (CIBERESP); University Hospitals Leuven, Department of Respiratory Diseases</p> <p>Costilla-Frias, Marcos; Universitat Pompeu Fabra (UPF); Universitat Autònoma de Barcelona (UAB)</p> <p>Louvaris, Zafeiris; National and Kapodistrian University of Athens, Faculty of Physical Education and Sports Sciences; KU Leuven, Department of Rehabilitation Sciences</p> <p>Gimeno-Santos, Elena; ISGlobal, Centre for Research in Environmental Epidemiology (CREAL); Universitat Pompeu Fabra (UPF); CIBER Epidemiología y Salud Pública (CIBERESP); Hospital Clínic de Barcelona, 8 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Pneumology department</p> <p>Tabberer, Maggie; GlaxoSmithKline</p> <p>Rabinovich, Roberto; The University of Edinburgh, 9 ELEGI/Colt laboratory, UoE/MRC Centre for Inflammation Research</p> <p>De Jong, Corina; University of Groningen, University Medical Center Groningen (UMCG), 11 GRIAC-Primary Care, department of general practice and elderly care; University of Groningen, University Medical Center Groningen (UMCG), 12 Groningen Research Institute for Asthma and COPD (GRIAC)</p> <p>Polkey, Michael; Royal Brompton and Harefield NHS Foundation Trust and Imperial College, NIHR Respiratory Biomedical Research Unit</p> <p>Hopkinson, Nicholas; Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, NIHR Respiratory Biomedical Research Unit</p> <p>Karlsson, Niklas; Astra Zeneca</p> <p>Serra Pons, Ignasi; ISGlobal, Centre for Research in Environmental Epidemiology (CREAL)</p> <p>Vogiatzis, Ioannis; National and Kapodistrian University of Athens, Faculty of Physical Education and Sports Sciences; Northumbria University, Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences</p> <p>Troosters, Thierry; KU Leuven, Department of Rehabilitation Sciences; University Hospitals Leuven, Department of Respiratory Diseases</p> <p>Garcia-Aymerich, Judith; ISGlobal, Centre for Research in Environmental Epidemiology (CREAL); Universitat Pompeu Fabra (UPF); CIBER</p> |

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|            | Epidemiología y Salud Pública (CIBERESP)  |
| Key Words: | COPD (clinical aspects), Exacerbations, physical activity, prospective study, PROactive |
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Manuscripts

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

Heleen Demeyer<sup>1,2,3,4,5\*</sup>, Marcos Costilla-Frias<sup>3,6\*</sup>, Zafeiris Louvaris<sup>1,7</sup>, Elena Gimeno-Santos<sup>2,3,4,8</sup>, Maggie Tabberer<sup>9</sup>, Roberto A. Rabinovich<sup>10</sup>, Corina de Jong<sup>11,12</sup>, Michael I. Polkey<sup>13</sup>, Nicholas S. Hopkinson<sup>13</sup>, Niklas Karlsson<sup>14</sup>, Ignasi Serra<sup>2,3,4</sup>, Ioannis Vogiatzis<sup>7,15</sup>, Thierry Troosters<sup>1,5</sup>, Judith Garcia-Aymerich<sup>2,3,4</sup>, on behalf of the PROactive Consortium<sup>16</sup>

\*Both authors contributed equally

### Affiliations:

- 1 KU Leuven, Department of Rehabilitation Sciences, B-3000 Leuven, Belgium
- 2 ISGlobal, Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
- 3 Universitat Pompeu Fabra (UPF), Barcelona, Spain
- 4 CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona
- 5 University Hospitals Leuven, Department of Respiratory Diseases, B-3000 Leuven, Belgium
- 6 Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
- 7 Faculty of Physical Education and Sports Sciences, National National and Kapodistrian University of Athens, Athens, Greece.
- 8 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic de Barcelona, Pneumology department, Barcelona, Spain
- 9 GlaxoSmithKline, Uxbridge, United Kingdom
- 10 ELEGI/Colt laboratory, UoE/MRC Centre for Inflammation Research, The University of Edinburgh, Edinburgh, United Kingdom
- 11 GRIAC-Primary Care, department of general practice and elderly care, University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands
- 12 Groningen Research Institute for Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands
- 13 Royal Brompton and Harefield NHS Foundation Trust and Imperial College, NIHR Respiratory Biomedical Research Unit, London, UK.
- 14 Astra Zeneca, Gothenburg, Sweden
- 15 Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University, Newcastle, United Kingdom

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2           <sup>16</sup> A full list of the PROactive consortium members and their affiliations can be found in the  
3           Acknowledgements section  
4

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6           **Corresponding author:** Judith Garcia-Aymerich, ISGlobal, Doctor Aiguader 88, 08003 Barcelona,  
7           Spain. E-mail: Judith.garcia@isglobal.org  
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10           **Take home message:** Exacerbations have a negative impact on long-term daily physical activity of  
11           COPD patients.  
12

13           **Keywords:** COPD, physical activity, exacerbations, prospective study.  
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16           Text Word count: 1198  
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18           Figures: 1  
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2 *To the editor*  
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4 Physical activity (PA) is a relevant outcome measure in COPD. Low PA is prevalent and drives  
5 prognosis [1]. Unfortunately, the determinants of PA and its change over time are poorly  
6 understood [1]. The fact that the PA progressively declines over time along with worsening of lung  
7 function and health status [2], suggests that the PA decline could be due to the progression of the  
8 disease and specifically to acute exacerbations [3]. An acute reduction in PA at the onset has been  
9 reported both in severe exacerbations requiring a hospitalization [4] and in ambulatory treated  
10 exacerbations [5,6]. A sustained PA reduction has been shown one month after hospital discharge  
11 [4] whereas PA almost returns to stable levels after community treated exacerbations [6]. One  
12 study found faster PA decline in patients with a history of  $\geq 2$  exacerbations in the 12 months prior  
13 to the study [5]. This analysis did not adjust for confounders of the association (*e.g.* airflow  
14 obstruction, symptom burden) or external variables influencing PA (*e.g.* climate). It could also be  
15 argued that the greater decline in PA was due to lower health status at baseline. Although PA is an  
16 important outcome for COPD patients, little is known about the role of exacerbations on patients'  
17 experience of PA. Importantly, both the amount of activity and difficulties experienced during  
18 activity are integral to the concept of PA limitation [7]. The aim of the present analysis was to  
19 assess the association between the number and severity of exacerbations and changes in PA and  
20 PA experience.  
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35 As part of the IMI-JU PROactive study [7,8], patients with COPD from mixed healthcare settings  
36 (tertiary hospitals, rehabilitation centres and primary care) in 5 European centres [Athens (Greece),  
37 Edinburgh and London (UK), Leuven (Belgium) and Groningen (The Netherlands)] were studied at  
38 baseline and at 12 months follow-up. Patients followed and those lost to follow-up were  
39 comparable. Objective PA was measured using the Dynaport Movemonitor accelerometer  
40 (McRoberts BV, The Hague, The Netherlands). The main PA outcome analysed was the change  
41 (difference between baseline and one year) in daily step count, the secondary outcome was the  
42 change in intensity during locomotion. Patient experience of PA was assessed with the Clinical visit  
43 PROactive Physical Activity in COPD (C-PPAC) instrument [7], which consists of a total score and  
44 amount and difficulty scores. The number and severity of COPD exacerbations during the 12-  
45 month follow-up was retrieved [8]. We defined exacerbations as moderate (treated in an  
46 ambulatory setting with systemic antibiotics and/or systemic glucocorticosteroids) or severe  
47 (requiring hospital admission), following the GOLD initiative guidelines [9]. In addition to the  
48 number of exacerbations, we generated a variable combining the number and the severity of  
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2 exacerbations. The association between exacerbation variables and PA change was analysed using  
3 regression analysis adjusted for baseline PA values. To remove the effect of potential confounders  
4 (see footnote Figure 1) we built a multivariable linear model for each PA outcome. Sensitivity  
5 analyses were performed excluding patients (i) with a COPD admission in the year before  
6 recruitment, (ii) with extreme PA values ( $\leq 5^{\text{th}}$  or  $\geq 95^{\text{th}}$  percentiles) and (iii) with a COPD admission  
7 2 months prior to the final measurement to exclude an acute effect. As post hoc explanatory  
8 analyses we tested the (bivariate) association between exacerbation variables and change in FEV<sub>1</sub>,  
9 6MWD and mMRC, adjusted for baseline. All statistical analyses were performed using SAS 9.4  
10 (SAS Institute Inc., Cary, NC, USA).  
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19 The present analysis is based on 141 patients with valid data at baseline and follow-up (75% male,  
20 with a mean (SD) of 67 (8) years, 27 (5) kg.m<sup>-2</sup> BMI, 59 (21) % predicted FEV<sub>1</sub>) of whom eighty-one  
21 (57%) experienced at least one exacerbation during follow-up. In the whole group there was a  
22 small, non-significant decline in step count [5209 (3050) steps.day<sup>-1</sup> at baseline vs 5019 (3099)  
23 steps.day<sup>-1</sup> at follow-up]; while movement intensity [1.82 (0.26) m.s<sup>-2</sup> at baseline vs 1.80 (0.28)  
24 m.s<sup>-2</sup> at follow-up], exercise capacity [452 (119) m at baseline vs 450 (123) m at follow-up] and  
25 FEV<sub>1</sub> [1.62 (0.69) l at baseline vs 1.63 (0.69) l at follow-up] did not change. Patients had a baseline  
26 mean C-PPAC total score of 69 (13), with domain scores for amount and difficulty 64 (16) and 74  
27 (15), respectively.  
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36 The number of exacerbations was related to the decline in steps.day<sup>-1</sup>. In the multivariable model,  
37 a mean (SE) change of 251 (207), -144 (262) and -797 (244) steps.day<sup>-1</sup> was observed in patients  
38 who had presented no, one, or two or more exacerbations during follow-up respectively (Figure  
39 1A). Patients experiencing two or more moderate exacerbations (-753 steps.day<sup>-1</sup>) and those  
40 experiencing at least one severe exacerbation (-705 steps.day<sup>-1</sup>), showed a larger decline in PA  
41 than those with no exacerbations (Figure 1B). There was no association between exacerbations  
42 during follow-up and changes in PA intensity (m.s<sup>-2</sup>). In relation to patient experience of PA, Figure  
43 1 (C,E) shows that patients with 2 or more exacerbations suffered more deterioration in C-PPAC  
44 amount (-4.2 points) and difficulty (-1.9 points) scores compared to patients having no or only one  
45 exacerbation. Patients experiencing two or more moderate exacerbations or at least one severe  
46 exacerbation showed a larger decline in C-PPAC amount and difficulty scores than those with no  
47 exacerbations, however some of these associations were not statistically significant (Figure 1 D,F).  
48 All sensitivity analyses yielded comparable results. Having exacerbations was related to a  
49 significant (p<0.01) larger increase in mMRC score but not to changes in 6MWD or FEV<sub>1</sub>.  
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2 The present analyses show that the acute drop in PA after an exacerbation [4,5,6] has an  
3 important and lasting effect that cannot be attributed to confounders or baseline PA. A higher  
4 exacerbation frequency was, as expected, associated with a more pronounced PA decline. Patients  
5 with frequent exacerbations constitute a specific disease phenotype with a worse prognosis,  
6 specifically a faster loss in lung function [10], a greater worsening of health status [11] and a  
7 substantial reduction in the amount of PA (-797 steps.day<sup>-1</sup>) as indicated by our findings. An  
8 unexpected finding from this study is that two or more moderate events result in a long-term  
9 decline that is clinically relevant [12] and equivalent to that of a severe event, confirming the  
10 importance of prevention and early management of exacerbations regardless of the severity [9].  
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18 The fact that exacerbations result in a decrease in the amount of PA can be interpreted as part of  
19 the multiple systemic consequences [9]. First, we could hypothesize that the decline is a  
20 consequence of a loss in exercise capacity. Against this hypothesis, our data fail to show an  
21 association between exacerbations during follow-up and changes in exercise capacity. Second, the  
22 PA decline could potentially be explained based on a worsening of symptoms during an  
23 exacerbation leading to more inactivity, bringing patients in a vicious cycle of symptoms and  
24 inactivity [13]. Based on our explanatory analysis showing an association between exacerbations  
25 and an increase in dyspnoea, the latter hypothesis would be a plausible mechanism.  
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33 The present results have important implications for daily clinical practice and underscore the  
34 importance of identifying frequent exacerbators, as supported by the combined GOLD  
35 classification [9]. Our results support the promotion of interventions to increase PA, such as  
36 coaching programs in the less [14] or pulmonary rehabilitation in the more severe patients [15]  
37 after an exacerbation.  
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## POTENTIAL CONFLICTS OF INTEREST

Thierry Troosters has served on advisory boards and his institution received speaker fees from BI, AZ, Novartis. Judith Garcia-Aymerich has received speaker fees from Esteve and her institution has received speaker fees from AZ, outside the submitted work. Michael Polkey has served on advisory boards for BI.



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## FIGURES

**Figure 1. Decline in steps.day<sup>-1</sup> (A-B) and C-PPAC instrument (D-F) according to COPD exacerbations in the 12-m follow-up (multivariable linear regression).**

Data presented as estimated marginal means (Least squares means) and SEM. Final models are adjusted for baseline physical activity and total CAT score. Other potential confounders (age, gender, smoking habit, BMI, any COPD admissions in previous 12 months, FEV<sub>1</sub> % predicted, FVC % predicted, FEV<sub>1</sub>/FVC ratio, ATS/ERS stage, 6MWD, mMRC and HADS anxiety and depression 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.

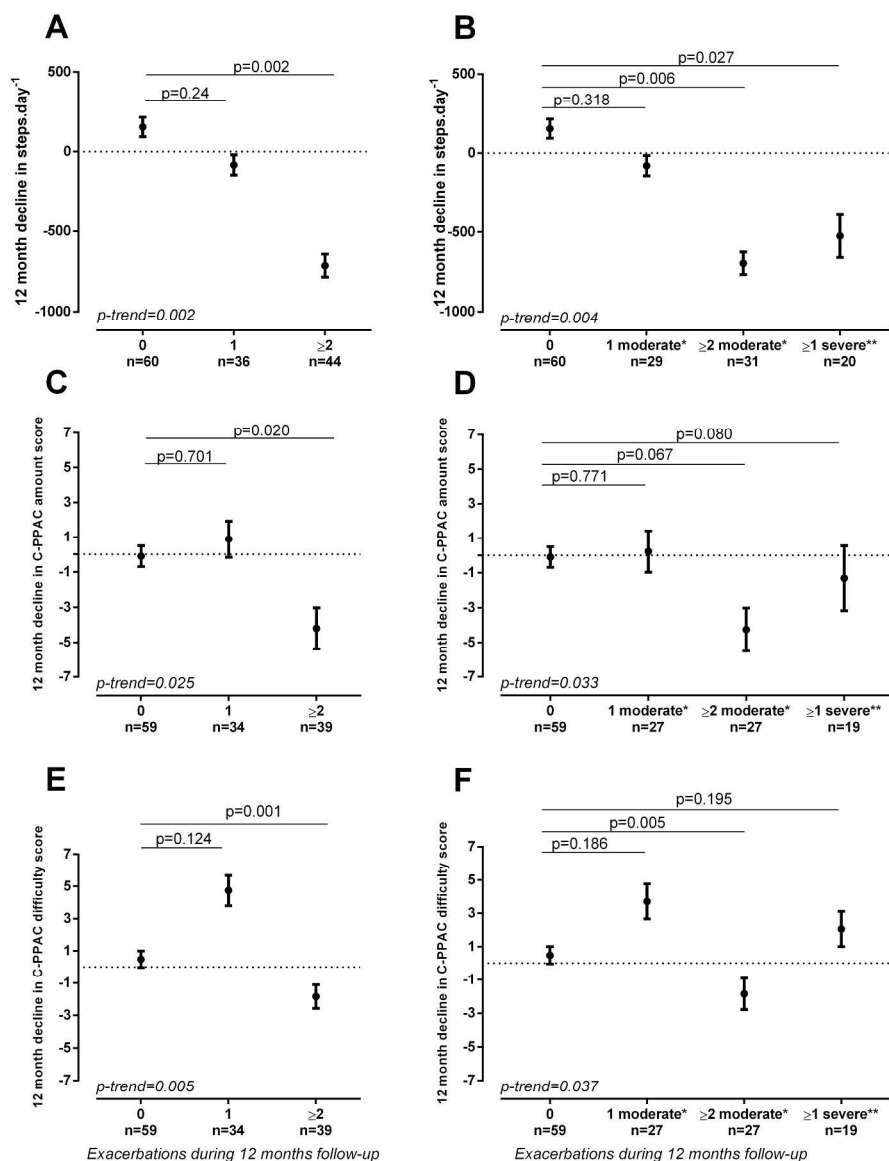


Figure 1. Decline in steps.day<sup>-1</sup> (A-B) and C-PPAC instrument (D-F) according to COPD exacerbations in the 12-m follow-up (multivariable linear regression).

Data presented as estimated marginal means (Least squares means) and SEM. Final models are adjusted for baseline physical activity and total CAT score. Other potential confounders (age, gender, smoking habit, BMI, any COPD admissions in previous 12 months, FEV<sub>1</sub> % predicted, FVC % predicted, FEV<sub>1</sub>/FVC ratio, ATS/ERS stage, 6MWD, mMRC and HADS anxiety and depression 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.

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9 Dear Prof. Fabbri,

10 Dear Prof. Humbert,

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12 Dear Prof. Dinh-Xuan,

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20 We would like to thank you for the interest in our paper “Both moderate and severe exacerbations  
21 accelerate physical activity decline in COPD patients” and for giving us the opportunity to resubmit this  
22 paper as a research letter. We are convinced that the research letter brings an important clinical  
23 message by showing the negative impact of COPD exacerbations on daily physical activity of COPD  
24 patients. The results underscore the relevance of identifying frequent exacerbators, as supported by  
25 the combined GOLD classification scheme.  
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33 The present research letter is in line with the ERJ guidelines and all authors have approved the final  
34 version. Results presented in this research letter have not been published previously, and no similar  
35 paper is in press or under review elsewhere.  
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41 On behalf of all authors,

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45 Yours sincerely,

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47 Dr. Judith Garcia-Aymerich, MD, FERS  
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51 A handwritten signature in black ink, appearing to be the initials 'JA' with a stylized flourish.  
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