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Patrones de progresión de la actividad física en pacientes con EPOC
Patterns of physical activity progression in patients with COPD

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Resumen:	We have uploaded the marked-up and unmarked Spanish Abstract as separate documents as the word count has slightly increased to 259 words following changes suggested by one of the Reviewers.
Respuesta a los revisores:	The 'Response to Reviewers' has been uploaded as a separate document because it contains tables which do not display correctly in this box and would therefore be lost in this format.

Jose Ignacio De Granda-Orive
Editor asociado
Archivos de Bronconeumología

July 24th, 2020

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript entitled:

Patrones de progresión de la actividad física en pacientes con EPOC
Patterns of physical activity progression in patients with COPD

The comments and suggestions of the Reviewers are much appreciated and have helped to improve the manuscript.

As suggested by Reviewer 3 we have specified now the pharmacological treatment for COPD in the manuscript and the related tables.

We have also replied to all other comments of the Reviewers as specified in the 'Response to Reviewers' and in the revised versions of the marked-up and unmarked manuscript. Please find attached also the graphical abstract to our manuscript.

The manuscript is not currently under consideration or accepted elsewhere. All authors have approved the revised version of the manuscript.

Thank you for your consideration.

Sincerely, on behalf of the authors,

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Patterns of physical activity progression in patients with COPD

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Authors' contribution

JGA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MK, HD and JGA drafted the first version of the manuscript; MK, HD, MB and JGA had full access to the data and were responsible for the statistical analysis; MK, HD, MB, AAE, EB, ABG, EGS, NH, CdJ, NK, ZL, MPo, MPu, RRa, RRo, PVC, IV, TT, JGA contributed to data collection and coordination. All authors 1) provided substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; 2) drafted or revised the manuscript for important intellectual content; 3) approved the final version; and 4) agreed to be accountable for all aspects of the work.

Declaration of interest

NK is employed by AstraZeneca. MP reports personal fees from Philips, during the conduct of the study. TT reports lecture fees to his institution from Boehringer Ingelheim, Chiesi Belgium and AstraZeneca outside the submitted work. JGA reports payments for consulting and lecture fees to her institution from AstraZeneca and lecture fees from Esteeve, Chiesi and Menarini outside the submitted work. The authors report no other conflict of interest in this work.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethics approval

This study was conducted in accordance with the amended Declaration of Helsinki. Both studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients.

The Urban Training trial was approved by the ethics committees of all participating institutions (Comitè Ètic d‘Investigació Clínica Parc de Salut MAR 2011/4291/I, Comitè

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The PROactive study was advised and approved by the PROactive ethics and patient advisory boards, and approved by the local ethics committee at each centre (Commissie medische ethiek van de universitaire ziekenhuizen KU Leuven (Leuven, S-55919); Medische ethische toetsingscommissie universitair medisch centrum Groningen (Groningen, Metc 2013.362); RES Committee London—South East (London and Edinburgh, 13/LO/1660); Scientific Council of the 'Sotiria' General Hospital for Chest Diseases (Athens, 27852/7-10-13); Kantonale Ethikkommission Zürich and Ethikkommission Nordwest- und Zentralschweiz (Zurich, KEK-ZH-Nr. 2013-0469).

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Title: Patrones de progresión de la actividad física en pacientes con EPOC

Patterns of physical activity progression in patients with COPD

We thank the Reviewers for the comments that have helped to improve the manuscript. All comments have been addressed below.

ANSWERS TO REVIEWER #1:

Comments to the Author

General Comments (R1)

R1
The authors present for the first time an evaluation of the natural change in physical activity over time in COPD patients, showing that it is heterogenous with three distinct groups identified over a 12 month follow up period. They further show that while most COPD patients are inactive at baseline and those that are clinically worse at baseline are more likely to stay in this group with follow up, determining which of the three distinct groups a patient will wind up in after 12 months of follow up is unpredictable. The authors do an excellent job reviewing the known literature, accessing the strengths and weaknesses of their work, and contextualizing it in the field. Excellent job.

We are happy and want to thank the Reviewer for such a positive consideration.

ANSWERS TO REVIEWER #2:

Comments to the Author

General Comments (R2)

R2
El presente estudio es muy bienvenido porque aporta conocimiento basado en evidencias firmes sobre la actividad física en pacientes con EPOC. Su utilidad es indudable por lo novedoso de los objetivos y el análisis planteado. Los resultados apoyan la necesidad de monitorización estrecha de la actividad física en estos pacientes porque no es predecible con las variables clínicas que solemos manejar, y las implicaciones en la enfermedad y su pronóstico, así lo aconsejan. Como bien destacan los autores, el estudio también demuestra la importancia de incluir a un grupo control en los estudios de intervención en actividad física. **Quiero felicitar a los autores por el estudio realizado, tanto por los objetivos planteados como por la metodología empleada. El texto está muy bien escrito, se sigue bien a pesar de la complejidad y la cantidad de datos que se aportan. También hay que reconocer que la discusión está muy bien planteada, en párrafos separados que facilitan la argumentación. Las conclusiones son la adecuadas a los resultados obtenidos.** **Las tablas son muy prolijas en datos y el material suplementario es también muy extenso, pero en mi opinión es reflejo del trabajo realizado y lo encuentro adecuado.**

We thank the Reviewer for her/his positive appraisal. We have addressed the comments as follows.

R2C1
ABSTRACT: El párrafo …" Usando Activo que reduce como referencia, menor distancia en la prueba de la marcha de 6 minutos…que aumenta" creo que no se entiende tan bienen español como en inglés. Sugiero este cambio: por cada 10 m menos y por cada punto mas.

We thank the Reviewer for noticing that this sentence does not read well in Spanish and have modified it in the revised version of the Abstract accordingly:

La distancia en la prueba de la marcha de 6 minutos (6MWD) y la disnea se asociaron independientemente con ser *Inactivo*: RRR [95% CI] 0.94 [0.90-0.98] por cada 10 m de 6MWD (p=0.001) y 1.71 [1.12-2.60] por cada punto en la escala mMRC (p=0.012), respectivamente, en comparación con el patrón *Activo que reduce*.

R2C2
INTRODUCCIÓN: En la frase "Given the heterogeneous nature and progression of COPD (19), it can be hypothesized that physical activity progression also displays different patterns, not captured by mean values." Mean values no está claro a qué se refiere. Es actividad física? Por favor, necesita aclaración.

We thank the Reviewer for pointing out that this phrase needed further clarification. We have changed the text in the Introduction section of our revised version accordingly:

Given the heterogeneous nature and progression of COPD (19), it can be hypothesized that physical activity progression also displays different patterns, not captured by the mean physical activity values.

R2C3
METODOLOGÍA: La muestra utilizada es heterogénea: nivel primario, hospitalario, etc., pero también en relación a la procedencia geográfica (Urban training Cataluña, España y la cohorte proActive, de diversos países europeos, no españoles). ¿Creen los autores que los resultados obtenidos pueden estar influidos por esta circunstancia, al haber agrupado a todos los pacientes en una única muestra? Sobre todo, porque los sistemas asistenciales sanitarios son diferentes según los países, por ejemplo. Un comentario al respecto en la discusión puede ser pertinente.

We agree with the Reviewer that pooling the Urban Training and the PROactive cohorts brings some heterogeneity to the overall study population. This fact is considered by the authors a strength of the current analysis. On one hand, including patients from diverse severity settings maximises the variability in physical activity levels and changes, and thus allows to identify “more representative”

patterns than just using a single recruitment setting/severity group. On the other hand, including patients from diverse geographic locations allows to indirectly control for residual confounding (e.g., unmeasured potential confounders that would distribute differently by setting). For the statistical analysis, we used a mixed effects model that accounts for possible heterogeneity in unmeasured characteristics related to study and city area.

As suggested by the Reviewer, we have added corresponding statements to the Methods and Discussion sections of our revised version.

Methods, Statistical analysis (in manuscript and supplement)

To assess determinants of physical activity progression patterns, we first compared subjects' characteristics by physical activity patterns and obtained p-values from mixed logistic regression models with random intercepts for study and city area to account ~~for the multi-level structure of the data~~ for possible heterogeneity in unmeasured characteristics related to study and city area.

Discussion

A major strength of our study is the inclusion of patients across a broad spectrum of disease severities and physical activity in several European cities. ~~making our results applicable to a large COPD population;~~ This makes our results applicable (i.e., more representative) to a larger COPD population than a single recruitment setting or severity group. In addition, the inclusion of patients from diverse geographic locations allowed us to indirectly control for residual confounding.

R2C4
METODOLOGÍA: **También es llamativo el nivel de mMRC medio, de menos de grado 2, lo que quiere decir que, a pesar de incluir pacientes con obstrucción grave y muy grave, la disnea es leve. ¿Esto puede haber influido en la actitud del paciente con EPOC a la hora de sus costumbres en actividad física?** **Igualmente sugiero hacer un comentario al respecto**

The Reviewer is right that the overall mMRC score of 1.3±0.9 is low. While we believe that this low score is related to the fact that we included patients from primary care, it indeed also means that even the patients with severe and very severe airflow limitation experienced relatively moderate

dyspnea (see Table A). We fully agree with the Reviewer that this may have positively influenced the physical activity levels of our patients.

Table A Dyspnea score (mMRC) by airflow limitation severity for the patients included in the present analysis (n=291).

Airflow limitation severity (post-bronchodilator FEV_1)	**n (%)**	**mMRC score (0-4)**
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	39 (13)	0.9±0.8
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	147 (51)	1.1±0.8
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	88 (30)	1.6±1.0
GOLD 4: Very Severe ($FEV_1 < 30\%$ predicted)	17 (6)	2.4±0.9

As suggested by the Reviewer we have modified the related statement in the Discussion section as follows:

The average lack of 12-month change in step count differs from previous studies that showed overall a decrease in physical activity (8,10,11,13). A potential explanation is that most of these studies recruited patients from outpatient or pulmonary clinics, which may have slightly more advanced disease and reduced variability in physical activity and COPD characteristics as compared to our sample including also primary care. Supporting this, the group of patients who started with a lower physical activity (59%) was similar in their baseline characteristics to previous studies and also had a comparable mean decrease of around 500 steps/day (10,11). Notably, the low overall dyspnea score may have positively influenced the physical activity level of our study population. A second explanation could lie in the high proportion of male subjects and regional differences in physical activity practice (a cohort of patients included in the Mediterranean region (5) had a baseline physical activity comparable to the Urban Training sample). These characteristics of our sample could justify the two patterns with relatively high baseline physical activity and an average small physical activity change.

ANSWERS TO REVIEWER #3:

Comments to the Author

General Comments (R3)

R3
Considero que se trata de un estudio interesante al clasificar a los pacientes EPOC en función del grado de actividad física.

We thank the Reviewer for her/his positive evaluation. We have addressed the comment as follows.

R3C1
Sin embargo considero que estos tres patrones de actividad física pueden estar influenciados por la intensidad de la intervención en cada paciente EPOC . Creo que se debería especificar en el trabajo el tipo de intervención farmacológica y no farmacológica (Rehabilitación) en todos los pacientes . Por ejemplo el adecuado tratamiento farmacológico o no de su enfermedad puede condicionar la actividad física . En conclusión creo que es un sesgo que hay que especificar.

The Reviewer is certainly right in pointing out that the pharmacological and non-pharmacological treatments for COPD may affect physical activity and that these treatments should be specified.

For the pharmacological treatment, we have therefore added the main classes of anti-obstructive therapy in line with the recommmendations of the GOLD report 2020 [1] to the Tables 1 and 2, as well as to the supplementary Table S1. The distribution of long-acting beta$_2$-agonists (LABA) or long-acting anti-muscarinics (LAMA) and of the combination treatment (inhaled corticosteroid with LABA and/or LAMA) was similar for all three patterns. Of note, specifically for *Active Improvers* and *Decliners* the pharmacological treatment was very comparable.

As concerns the non-pharmacological treatment, the percentage of patients in a pulmonary rehabilitation program at baseline or during follow-up was low (5% and 6%, respectively, Table 1). Due to the small numbers, we unfortunately could not test the role of pulmonary rehabilitation for the progression patterns. However, for sensitivity analysis we repeated the clustering after excluding patients in pulmonary rehabilitation programs at baseline or follow-up which confirmed the results of the main analysis (supplementary Table S5).

We have addressed the pharmacological treatment now in the Methods and Discussion section as well as in the Tables 1, 2 and supplementary Table S1. As results about non-pharmacological treatment are already presented in the manuscript and the supplement, we suggest no changes in this regard.

Methods

(iv) clinical: post-bronchodilator FEV_1 and FVC, the 6-min walking distance (6MWD) test, the COPD Assessment test (CAT), the Clinical COPD Questionnaire (CCQ), the modified Medical Research Council dyspnea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months and during follow-up, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance, comorbidities from medical records, pharmacological treatment for COPD, pulmonary rehabilitation at baseline and follow-up, incident diseases during follow-up, and knowledge of baseline physical activity (ie report on request);

Discussion

Most tellingly, we did not identify any factors that could predict among *Active* patients, the evolution to *Improvers* or *Decliners*. Surprisingly, the presence of severe exacerbations during follow-up did not play any role. It could be speculated that our harmonized exacerbation data was not detailed enough to distinguish the severity of exacerbations, the length of hospital stay or the time from the last exacerbation to physical activity assessment at follow-up. We also considered the role of incident comorbidities during follow-up, which could have influenced behavior, but they were not significantly different for the three patterns. Pharmacological treatment for COPD was not different across progression patterns discarding any potential role for treatment inappropriateness. Moreover, we did not find an association between the recruitment season and physical activity progression. This is in line with the hypothesis that the recruitment season, although possibly affecting the baseline levels of physical activity (12,18,33), would not affect the progression pattern during a follow-up of 12 months. Finally, we did not find an effect of accumulated rainfall on physical activity progression, as recently described cross-sectionally in the same PROactive population (14).

Table 1 Patient characteristics at baseline and at 12-month follow-up for all patients (n=291) and by study group (Urban Training and PROactive study).

	All patients	Urban Training study	PROactive study
	n = 291 (100%)	n = 148[a] (51%)	n = 143[a] (49%)
Sociodemographic			
Age (years)	68±8	69±8	67±8
Sex (men)	237 (81)	130 (88)	107 (75)
Current smoker	52 (18)	30 (20)	22 (15)
Pack-years	58±41	60±45	56±37
Education, high school or higher	168 (58)	49 (33)	119 (83)
Interpersonal			
Living with a partner[b]	216 (74)	124 (84)	92 (65)
Active worker[c]	36 (12)	16 (11)	20 (14)
Grandparenting[d]	67 (45)	67 (45)	-
Dog walking[d]	20 (14)	20 (14)	-
Environmental			
Recruitment season			
Spring	35 (12)	35 (24)	0 (0)
Summer	58 (20)	15 (10)	43 (30)
Fall	154 (53)	54 (36)	100 (70)
Winter	44 (15)	44 (30)	0 (0)
Average rainfall (h/day)[e,f]	0.62 (0.30-1.13)	-	0.62 (0.30-1.13)
Urban vulnerability index (from 0 -lowest to 1 –highest)[d,g]	0.637±0.175	0.637±0.175	-
Clinical			
FEV_1 (% predicted)	58.6±19.3	58.2±17.6	59.0±21.0
FEV_1/FVC ratio	0.51±0.13	0.55±0.12	0.48±0.13
Airflow limitation severity (post-bronchodilator FEV_1)			
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	39 (13)	15 (10)	24 (17)
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	147 (51)	80 (54)	67 (47)
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	88 (30)	45 (30)	43 (30)
GOLD 4: Very Severe ($FEV_1 < 30\%$ predicted)	17 (6)	8 (6)	9 (6)
6MWD (meters)	477±103	501±83	452±116
CAT score (0–40)	12.9±7.6	12.2±7.6	13.6±7.5
CCQ score (0-6)	1.55±0.98	1.40±0.95	1.70±0.98
C-PPAC amount score (0-100)	69.0±15.8	74.7±14.9	63.8±14.9
C-PPAC difficulty score (0-100)	78.4±14.5	82.7±13.4	74.5±14.5
C-PPAC total score (0-100)	73.7±12.8	78.7±11.5	69.2±12.3
mMRC score (0-4)	1.3±0.9	1.1±0.8	1.5±1.0
Any COPD exacerbation with hospital admission in previous 12 months	34 (12)	12 (8)	22 (15)
BMI (kg/m^2)	27.6±4.6	28.3±4.6	26.8±4.6
FFMI (kg/m^2)	19.0±3.0	19.6±3.2	18.4±2.8
Cardiovascular disease[h]	176 (60)	90 (61)	86 (60)
Ischemic heart disease[h]	29 (10)	13 (9)	16 (11)
Diabetes mellitus[h]	51 (18)	38 (26)	13 (9)
LABA or LAMA, alone	41 (14)	23 (16)	18 (13)
Inhaled corticosteroid with LABA and/or LAMA	179 (62)	80 (54)	99 (71)
Pulmonary rehabilitation at baseline	15 (5)	6 (4)	9 (6)
Knowledge of baseline PA	19 (7)	19 (13)	0 (0)
Psychological			
Anxiety (HAD-A, 0-21)	5±4	5±4	5±4
Depression (HAD-D, 0-21)	4±3	3±3	5±3
Physical activity			
Step count (steps/day)	6720±3667	7783±3847	5619±3121
Time in moderate-to-vigorous physical activity (≥3 METs; min/day)	99.4±45.3	109.1±45.7	89.4±42.8
Intensity during walking (m/s^2)	1.86±0.31	1.88±0.32	1.84±0.29
Sedentary time (h/day)	10.53±1.94	10.43±1.48	10.64±2.31
Wearing time (h/day)	14.73±1.56	14.64±0.54	14.81±2.16
Follow-up data			
Any COPD exacerbation with hospital admission during follow-up	28 (10)	10 (7)	18 (13)

Any incident comorbidity during follow-up[d,i]	34 (23)	34 (23)	-
Pulmonary rehabilitation during follow-up	16 (6)	6 (4)	10 (7)
Wearing time at follow-up (h/day)	14.52±1.63	14.60±0.61	14.43±2.24

Notes: Data are presented as n (%), mean±SD or median (interquartile range).

[a]Some variables have missing values, as follows. Urban Training: 1 in education, 25 in C-PPAC scores, 1 in any COPD exacerbation with hospital admission in previous 12 months, 18 in FFMI, 2 in HAD anxiety and depression, 5 in any COPD exacerbation with hospital admission during follow-up, 2 in pulmonary rehabilitation during follow-up; PROactive: 1 in living with a partner, 21 in average rainfall, 1 in CAT score, 1 in CCQ score, 6 in C-PPAC scores, 8 in FFMI, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in pulmonary rehabilitation during follow-up.
[b]marital status: living with a partner vs single, widowed or divorced.
[c]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.
[d]only available for Urban Training.
[e]only available for PROactive.
[f]average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.
[g]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.
[h]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.
[i]incident comorbidities included ICD10 codes C00 to N99.
Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale – Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression; MET: metabolic equivalent of task.

Table 2 Patient characteristics by physical activity progression pattern (*Inactive, Active Improvers* and *Active Decliners*) in 291 COPD patients.

	Inactive	***Active Improvers***	***Active Decliners***	**p-value for *Inactive* vs *Active Improvers* and *Decliners*[b]**	**p-value for *Active Improvers* vs *Decliners*[b]**
	n = 173[a] (59%)	**n = 49[a] (17%)**	**n = 69[a] (24%)**		
Urban Training study	59 (34)	39 (80)	50 (72)		
PROactive study	114 (66)	10 (20)	19 (28)		
Sociodemographic					
Age (years)	68±8	69±9	67±7	0.282	0.079
Sex (men)	137 (79)	41 (84)	59 (86)	0.931	0.789
Current smoker	33 (19)	5 (10)	14 (20)	0.152	0.152
Pack-years	60±38	63±52	49±40	0.187	0.082
Education, high school or higher	124 (72)	20 (42)	24 (35)	**0.006**	0.452
Interpersonal					
Living with a partner[c]	115 (66)	42 (88)	59 (86)	**0.017**	0.714
Active worker[d]	18 (10)	6 (12)	12 (17)	0.088	0.454
Grandparenting[e]	20 (34)	21 (54)	26 (52)	**0.039**	0.863
Environmental					
Average rainfall (h/day)[f,g]	0.63 (0.33-1.13)	0.90 (0.57-1.47)	0.33 (0.23-1.00)	0.877	0.329
Urban vulnerability index (from 0 -lowest to 1 –highest)[e,h]	0.646±0.176	0.613±0.200	0.646±0.153	0.312	0.369
Clinical					
FEV_1 (% predicted)	55.9±19.8	62.9±15.8	62.4±19.5	**0.001**	0.875
FEV_1/FVC ratio	0.48±0.14	0.55±0.11	0.55±0.11	**0.004**	0.904
6MWD (meters)	446±105	521±90	524±78	**<0.001**	0.861
CAT score (0-40)	14.2±7.7	11.5±7.3	10.5±6.6	**0.002**	0.435
CCQ score (0-6)	1.74±0.97	1.23±0.91	1.29±0.93	**0.001**	0.780
C-PPAC difficulty score (0-100)[i]	74.9±14.7	82.6±13.6	84.8±11.6	**<0.001**	0.380
mMRC score (0-4)	1.5±1.0	1.0±0.8	0.9±0.7	**<0.001**	0.329
Any COPD exacerbation with hospital admission in previous 12 months	24 (14)	4 (8)	6 (9)	0.517	0.918
BMI (kg/m^2)	27.6±5.0	27.5±3.9	27.5±4.2	0.139	0.999
FFMI (kg/m^2)	18.9±3.0	19.3±2.9	19.0±3.1	0.650	0.591
Cardiovascular disease[j]	109 (63)	28 (57)	39 (57)	0.221	0.930
Ischemic heart disease[j]	18 (10)	5 (10)	6 (9)	0.898	0.807
Diabetes mellitus[j]	23 (13)	11 (22)	17 (25)	0.412	0.786
LABA or LAMA, alone	24 (14)	7 (14)	10 (15)	0.796	0.949
Inhaled corticosteroid with LABA and/or LAMA	115 (67)	28 (57)	36 (53)	0.311	0.658
Psychological					
Anxiety (HAD-A, 0-21)	5±4	5±3	5±4	0.755	0.774
Depression (HAD-D, 0-21)	5±3	3±3	3±3	**0.009**	0.992
Follow-up data					
Any COPD exacerbation with hospital admission during follow-up	19 (11)	4 (8)	5 (7)	0.759	0.846
Any incident comorbidity during follow-up[e,k]	10 (17)	10 (26)	14 (28)	0.191	0.804

Notes: Data are presented as n (%), mean±SD or median (interquartile range).

[a]Some variables have missing values, as follows. *Inactive*: 15 in average rainfall, 1 in CAT total, 1 in CCQ score, 14 in C-PPAC difficulty score, 17 in FFMI, 2 in LABA or LAMA, alone, 2 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in any COPD exacerbation with hospital admission during follow-up; *Active Improvers*: 1 in education, 1 in

living with a partner, 2 in average rainfall, 5 in C-PPAC difficulty score, 4 in FFMI, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up; *Active Decliners*: 4 in average rainfall, 12 in C-PPAC difficulty score, 1 in any COPD exacerbation with hospital admission in previous 12 months, 5 in FFMI, 1 in LABA or LAMA, alone, 1 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up.

[b]p-value from mixed logistic regression models with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).

[c]marital status: living with a partner vs single, widowed or divorced.

[d]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.

[e]only available for Urban Training.

[f]only available for PROactive.

[g]average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.

[h]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.

[i]only C-PPAC difficulty is provided as C-PPAC amount and total score include steps/day which were used for the generation of the PA patterns and therefore cannot be assessed as predictors.

[j]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.

[k]incident comorbidities included ICD10 codes C00 to N99.

Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale - Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression.

Table S1 Patient characteristics at baseline for all patients (Urban Training and PROactive study, n=412) and for patients with 12-month follow-up vs lost-to follow-up.

	All patients	Follow-up	Lost-to follow-up	p-value[b]
	n = 412 (100%)	n = 291[a] (71%)	n = 121[a] (29%)	
Sociodemographic				
Age (years)	68±8	68±8	68±8	0.745
Sex (men)	316 (77)	237 (81)	79 (65)	**0.001**
Current smoker (yes)	77 (19)	52 (18)	25 (21)	0.508
Pack-years	58±41	58±41	60±41	0.684
Education, high school or higher	236 (57)	168 (58)	68 (56)	0.746
Interpersonal				
Living with a partner[c]	291 (71)	216 (74)	75 (63)	**0.016**
Active worker[d]	47 (11)	36 (12)	11 (9)	0.342
Grandparenting[e]	89 (43)	67 (45)	22 (39)	0.389
Dog walking [e]	26 (13)	20 (14)	6 (11)	0.566
Environmental				
Recruitment season				
Spring	55 (13)	35 (12)	20 (16)	
Summer	82 (20)	58 (20)	24 (20)	0.161
Fall	218 (53)	154 (53)	64 (53)	
Winter	57 (14)	44 (15)	13 (11)	
Urban vulnerability index (from 0 -lowest to 1 –highest)[e,f]	0.642±0.178	0.637±0.175	0.655±0.186	0.514
Clinical				
FEV_1 (% predicted)	57.7±18.9	58.6±19.3	55.6±17.9	0.140
FEV_1/FVC ratio	0.51±0.13	0.51±0.13	0.51±0.13	0.699
Airflow limitation severity (post-bronchodilator FEV_1)				
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	52 (13)	39 (13)	13 (11)	
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	207 (50)	147 (51)	60 (50)	0.259
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	125 (30)	88 (30)	37 (30)	
GOLD 4: Very Severe (FEV_1 <30% predicted)	28 (7)	17 (6)	11 (9)	
6MWD (meters)	461±109	477±103	421±111	**<0.001**
CAT score (0–40)	13.3±7.5	12.9±7.6	14.2±7.3	0.094
CCQ score (0-6)	1.59±0.98	1.55±0.98	1.69±0.98	0.172
C-PPAC amount score (0-100)	67.8±16.9	69.0±15.8	64.2±19.5	**0.024**
C-PPAC difficulty score (0-100)	77.9±14.9	78.4±14.5	76.3±16.0	0.269
C-PPAC total score (0-100)	72.8±13.6	73.7±12.8	70.3±15.4	**0.044**
mMRC score (0-4)	1.4±1.0	1.3±0.9	1.7±1.1	**<0.001**
Any COPD exacerbation with hospital admission in previous 12 months	49 (12)	34 (12)	15 (13)	0.781
BMI (kg/m^2)	27.7±5.2	27.6±4.6	28.1±6.3	0.306
FFMI (kg/m^2)	18.8±3.2	19.0±3.0	18.4±3.5	0.086
Cardiovascular disease[g]	240 (59)	176 (60)	64 (54)	0.212
Ischemic heart disease[g]	40 (10)	29 (10)	11 (9)	0.823
Diabetes mellitus[g]	73 (18)	51 (18)	22 (18)	0.817
LABA or LAMA, alone	56 (14)	41 (14)	15 (13)	0.686
Inhaled corticosteroid with LABA and/or LAMA	256 (63)	179 (62)	77 (65)	0.557
Pulmonary rehabilitation at baseline	25 (6)	15 (5)	10 (8)	0.233
Knowledge of baseline PA	24 (6)	19 (7)	5 (4)	0.348
Psychological				
Anxiety (HAD-A, 0-21)	5±4	5±4	6±4	0.117
Depression (HAD-D, 0-21)	4±3	4±3	4±4	0.210
Physical activity				
Step count (steps/day)	6415±3678	6720±3667	5682±3613	**0.010**
Time in moderate-to-vigorous physical activity (≥3 METs; min/day)	95.8±45.9	99.4±45.3	87.0±46.2	**0.013**
Intensity during walking (m/s^2)	1.84±0.31	1.86±0.31	1.80±0.30	**0.050**
Sedentary time (h/day)	10.53±1.93	10.53±1.94	10.52±1.92	0.961

Notes: Data are presented as n (%), mean±SD.

[a]Some variables have missing values, as follows. Follow-up: 1 in education, 1 in living with a partner, 1 in CAT total, 1 in CCQ score, 31 in C-PPAC scores, 1 in any COPD exacerbation with hospital admission in previous 12 months, 26 in FFMI, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 3 in HAD anxiety and depression; Lost-to follow-up: 1 in living with a partner, 1 in 6MWD, 33 in C-PPAC scores, 3 in any COPD exacerbation with hospital admission in previous 12 months, 5 in FFMI, 2 in ICD10 codes: I00 to I99 for Cardiovascular diseases; I20 to I25 for Ischemic heart disease, E14 for Diabetes mellitus, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD depression.

[b]p-value from mixed logistic regression models with random effects for study (Urban Training and PROactive), due to small numbers random effects for city area were not applied.

[c]marital status: living with a partner vs single, widowed or divorced.

[d]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.
[e]only available for Urban Training.
[f]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.
[g]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.
Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale - Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression; MET: metabolic equivalent of task.

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Patterns of physical activity progression in patients with COPD

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Abstract

Introduction: Although mean physical activity in COPD patients declines by 400 to 500 steps/day annually, it is unknown whether the natural progression is the same for all patients. We aimed to identify distinct physical activity progression patterns using a hypothesis-free approach and to assess their determinants.

Methods: We pooled data from two cohorts (usual care arm of Urban Training [NCT01897298] and PROactive initial validation [NCT01388218] studies) measuring physical activity at baseline and 12 months (Dynaport MoveMonitor). We identified clusters (patterns) of physical activity progression (based on levels and changes of steps/day) using k-means, and compared baseline sociodemographic, interpersonal, environmental, clinical and psychological characteristics across patterns.

Results: In 291 COPD patients (mean±SD 68±8 years, 81% male, FEV_1 59±19%$_{pred}$) we identified three distinct physical activity progression patterns: *Inactive* (n=173 [59%], baseline: 4621±1757 steps/day, 12-month change (Δ): -487±1201 steps/day), *Active Improvers* (n=49 [17%], baseline: 7727±3275 steps/day, Δ: +3378±2203 steps/day) and *Active Decliners* (n=69 [24%], baseline: 11267±3009 steps/day, Δ: -2217±2085 steps/day). After adjustment in a mixed multinomial logistic regression model using *Active Decliners* as reference pattern, a lower 6-min walking distance (RRR [95% CI] 0.94 [0.90-0.98] per 10m, p=0.001) and a higher mMRC dyspnea score (1.71 [1.12-2.60] per 1 point, p=0.012) were independently related with being *Inactive.* No baseline variable was independently associated with being an *Active Improver*.

Conclusions: The natural progression in physical activity over time in COPD patients is heterogeneous. While *Inactive* patients relate to worse scores for clinical COPD characteristics, *Active Improvers* and *Decliners* cannot be predicted at baseline.

Keywords

COPD, physical activity, patterns of progression, cluster analysis, determinants

Abbreviations

BMI, body mass index; CAT, COPD assessment test; CCQ, clinical COPD questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; C-PPAC, clinical visit—PROactive physical activity in COPD; FEV1, forced expiratory volume in 1 second; FFMI, fat free mass index; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HAD-A, hospital anxiety and depression scale – anxiety; HAD-D, hospital anxiety and depression scale – depression; LABA: long-acting beta$_2$-agonists; LAMA: long-acting anti-muscarinics; MET, metabolic equivalent of task; mMRC, modified medical research council dyspnea score; 6MWD, 6-min walking distance; MVPA, moderate to vigorous physical activity; RRR, relative risk ratio; SD, standard deviation.

Introduction

Physical activity is a key prognostic factor in chronic obstructive pulmonary disease (COPD), yet poorly understood. COPD patients are less active than healthy controls from the early stages of disease onwards (1–3) and this reduced activity has been associated with impaired prognosis and accelerated progression of COPD (4,5). For this reason, several national and international COPD guidelines recommend encouraging patients to maintain a good physical activity level (6,7).

Despite patients' and health professionals' efforts, physical activity has been shown to exhibit a spontaneous decline of an average of 400 to 500 steps/day per year in COPD patients (8–14). Such observed decline has been related, although not consistently, to lower lung function levels (10,11), the presence of exacerbations (15–17) or the seasonality of testing (eg, decline observed in patients going from summer to winter) (12,18). Given the heterogeneous nature and progression of COPD (19), it can be hypothesized that physical activity progression also displays different patterns, not captured by the mean physical activity values. Two previous studies support this hypothesis by showing distinct physical activity trajectories over 9 months after a pulmonary rehabilitation program (20,21). However, the reported progression in physical activity after rehabilitation programs probably does not reflect how physical activity evolves in the wider COPD population nor in an observational setting, where patients receive a variable combination of pharmacological and non-pharmacological treatments.

We aimed (1) to identify, using a hypothesis-free approach, distinct patterns of natural physical activity progression in COPD patients recruited from diverse settings (primary care, hospital and rehabilitation services) and followed during 12 months; and (2) to

assess the baseline sociodemographic, interpersonal, environmental, clinical and psychological determinants for the identified patterns. Better understanding of the natural progression of physical activity, of potential distinct patterns and of their determinants could help to individualize strategies to increase (or prevent a decline in) physical activity.

Methods

Study design and patient population

This was an observational (no intervention) cohort study of 12-month follow-up including patients from: (1) the usual care arm (n=205) from the Urban Training study (22), that recruited patients from primary care and tertiary hospitals in five Catalan seaside municipalities (Badalona, Barcelona [center and shore areas], Mataró, Viladecans and Gavà); and (2) the clinically stable patients (n=207) from the PROactive validation study (23), that recruited patients from primary care settings, rehabilitation centers and tertiary hospitals in five European cities (Athens/Greece, Edinburgh and London/United Kingdom, Groningen/Netherlands, and Leuven/Belgium). Both studies defined COPD according to ATS/ERS (post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.70) (24). Patients were included in the present analyses if they had a valid physical activity measure (see below) at baseline and 12-month follow-up.

Both studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients.

Physical activity measurements

Physical activity was objectively measured using the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands) (25) for one week at baseline and follow-up. In Urban Training, patients wore the monitor for 24 hours and data during waking hours (from 07:00 h to 22:00 h) were retrieved. In PROactive, patients wore the device during waking hours. A valid physical activity measurement was defined as a minimum of three days with at least 8 hours of wearing time within waking hours for both studies (26); details have been previously published (22,23). A physical activity report was provided to patients if requested.

We used step count as the primary outcome to define physical activity progression patterns, and time spent in physical activity of moderate to vigorous intensity (MVPA, ≥3 METs [metabolic equivalents of tasks] min/day), movement intensity (m/s^2) during walking, and sedentary time (sum of lying and sitting time, hours/day) as secondary physical activity outcomes to describe patterns. Physical activity experience was assessed by the amount, difficulty and total scores of the Clinical visit-PROactive Physical Activity in COPD (C-PPAC) tool (23).

Other measurements

We used variables available from both studies (ie exactly the same or equivalent standardized questions and procedures had been used) or variables that were available from one study only but had been related to physical activity or its evolution in the literature: (i) sociodemographic: age, sex, smoking history and education; (ii) interpersonal: marital status, working status, grandparenting and dog walking; (iii) environmental: season of recruitment, average yearly rainfall and urban vulnerability index (a measure of socioeconomic status at the census tract level); (iv) clinical: post-

bronchodilator FEV_1 and FVC, the 6-min walking distance (6MWD) test, the COPD Assessment test (CAT), the Clinical COPD Questionnaire (CCQ), the modified Medical Research Council dyspnea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months and during follow-up, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance, comorbidities from medical records, pharmacological treatment for COPD, pulmonary rehabilitation at baseline and follow-up, incident diseases during follow-up, and knowledge of baseline physical activity (ie report on request); and (v) psychological: the Hospital Anxiety (HAD-A) and Depression (HAD-D) scores. Full details on study procedures and quality control have been reported previously (22,23,27).

Statistical analysis

Sample size calculations, missing data strategy and full statistical analyses are provided in the supplement.

We identified cluster groups (physical activity patterns) using k-means (28), a hypothesis-free method that allowed grouping patients based on the baseline level, the final level and the change in daily step count. To characterize the patterns, we described physical activity and physical activity experience variables according to the cluster groups and compared baseline to follow-up values by paired t-tests.

To assess determinants of physical activity progression patterns, we first compared subjects' characteristics by physical activity patterns and obtained p-values from mixed logistic regression models with random intercepts for study and city area to account ~~for the multi-level structure of the data~~ for possible heterogeneity in unmeasured

characteristics related to study and city area. Then we built a multivariable multinomial regression model using the generalized linear latent and mixed model, with also random intercepts for study and city (29). Model building combined step-forward and backward algorithms and we tested goodness of fit of the final model.

As sensitivity analyses, we (1) repeated cluster analysis separately for Urban Training and PROactive; (2) tested the association between the change in daily step count and the change in wearing time overall and per pattern; and (3) repeated the clustering after excluding patients included in pulmonary rehabilitation programs at baseline and/or during follow-up.

All analyses were conducted using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

Results

From 412 patients at baseline, 291 (71%) completed the follow-up visit and were included in the current analyses (Figure S1). These patients had a higher proportion of males, better functional status and were more active at baseline than those lost-to follow-up (Table S1). Included patients were 81% male and had a mean age of 68 years, FEV_1 of 59% predicted, 6MWD of 477 m, mMRC dyspnea score of 1.3, and walked 6720 steps/day (Table 1). Compliance with the activity monitor during waking hours was excellent: at baseline median (range) valid days of 7 (3-7) and mean±SD wearing hours of 14.6±0.5 in Urban Training, and 6 (3-7) days and 14.6±0.5 wearing hours in PROactive; and at follow-up, 7 (4-7) days and 14.6±0.6 wearing hours in Urban Training, and 6 (3-7) days and 14.8±2.2 wearing hours in PROactive.

At the group level, the step count did not change over 12 months. In the hypothesis-free approach, we identified three cluster groups (three distinct physical activity patterns) (Figure 1, Table S2). A first cluster (n=173 [59%]), labelled *Inactive* pattern due to the low step count, walked at baseline mean±SD 4621±1757 steps/day and decreased their physical activity by 487±1201 steps/day over 12 months. A second cluster (n=49 [17%]), labelled *Active Improvers*, walked 7727±3275 steps/day at baseline and increased by 3378±2203 steps/day. The third cluster (n=69 [24%]), labelled *Active Decliners*, walked 11267±3009 steps/day at baseline and decreased by 2217±2085 steps/day. Distribution of MVPA and walking intensity by physical activity pattern followed the same sequence as steps/day, except for walking intensity in *Active Improvers* that did not change. Sedentary time did not change for *Inactive*, decreased for *Active Improvers* and increased moderately for *Active Decliners*. The physical activity experience as expressed by C-PPAC scores did not change for the *Inactive* pattern; the *Active Improvers* increased the C-PPAC scores (ie, increased amount and reduced difficulty); the *Active Decliners* decreased the C-PPAC amount and total scores while the C-PPAC difficulty score did not change (Figure 2, Table S2).

Patients in the *Inactive* physical activity pattern had a higher degree of education, a smaller proportion was living with a partner or grandparenting, and they presented with a worse general health status, lower lung function, poorer exercise capacity, worse quality of life and higher dyspnea and depression scores than those in the *Active Improvers* or *Decliners* patterns (Table 2). *Active Improvers* and *Decliners* were very similar in their baseline characteristics, except for their daily step count.

In the multivariable multinomial logistic regression model we used *Active Decliners* as the reference pattern to capture both the determinants of being *Inactive vs Active* and the

determinants of being an *Active Improver vs Decliner*. A lower exercise capacity and a higher mMRC dyspnea score were independently related with being *Inactive* whereas no variable was identified as independently associated with being an *Active Improver* (Table 3). The final model showed good fit. Sensitivity analyses confirmed the results (Tables S3, S4 and S5).

Discussion

This study identified, for the first time to our knowledge, the natural progression of physical activity in COPD patients. We used a hypothesis-free approach that allowed the identification of patterns without *a priori* assumptions about the physical activity changes over time. We found that (1) the natural change in physical activity over time was indeed heterogeneous; (2) the majority of patients (59%) was inactive at baseline and decreased their physical activity level subsequently; (3) among active individuals some increased and some decreased their physical activity level; and (4) although clinical COPD characteristics were related to the physical activity level at baseline they could not predict subsequent physical activity changes.

A first important finding is that physical activity progression in COPD is heterogeneous. In our 12-month study, mean changes in the full group were virtually zero; however when using hypothesis-free clustering methods, we identified one *Inactive* pattern which decreased and two *Active* patterns which increased or decreased physical activity. This observation is in line with previous reports of heterogeneous physical activity progression in patients with rheumatoid arthritis (30). The average lack of 12-month change in step count differs from previous studies that showed overall a decrease in physical activity (8,10,11,13). A potential explanation is that most of these studies recruited patients from outpatient or pulmonary clinics, which may have slightly more

advanced disease and reduced variability in physical activity and COPD characteristics as compared to our sample including also primary care. Supporting this, the group of patients who started with a lower physical activity (59%) was similar in their baseline characteristics to previous studies and also had a comparable mean decrease of around 500 steps/day (10,11). Notably, the low overall dyspnea score may have positively influenced the physical activity level of our study population. A second explanation could lie in the high proportion of male subjects and regional differences in physical activity practice (a cohort of patients included in the Mediterranean region (5) had a baseline physical activity comparable to the Urban Training sample). These characteristics of our sample could justify the two patterns with relatively high baseline physical activity and an average small physical activity change.

The second important finding is that there seems to exist a group of COPD patients (our *Active Improvers*) that spontaneously increase their physical activity over time. Of note, such observed increase of >3000 steps/day is remarkably high given that the minimal important difference has been proposed between 600 and 1100 steps/day (31). There are several possibilities that would explain this observed increase. First, some patients could have been inactive at baseline by chance; however, we tested this option against study records by screening for atypical events and it did not hold true. Second, regression to the mean could account for part of the increase, but in our data regression to the mean was estimated to account for maximal 25% of the effect. Third, changes in daily steps could be due to changes in wearing time, but this was not the case in our study (Table S4). Fourth, patients could have increased their physical activity after participation in rehabilitation programs, but this was dismissed in our analysis (Table S5). Finally, we considered that some patients in the usual care arm of Urban Training could have increased their physical activity due to being enrolled in a physical activity

study. However, the proportion of patients from Urban Training was similar between *Active Improvers* and *Active Decliners*. Thus, we suggest that some patients do actually increase their physical activity.

The evolution of other physical activity variables provided complementary information. Time in MVPA and sedentary time (opposite direction) paralleled the progression of step count in all three patterns, supporting previous research that suggested that in COPD patients, physical activity and sedentary time provide information about the same concept (5). We also investigated the progression of physical activity from the perspective of patients. As expected, C-PPAC amount and total scores followed a trend similar to the objectively measured physical activity, as they include steps/day in their calculation. However, C-PPAC difficulty score remained unchanged in *Inactive* and *Active Decliners* and increased (ie, less difficulty) in *Active Improvers*, suggesting that the observed increase in amount could be related to experiencing fewer difficulties (less dyspnea for instance (32)) while being active.

Our third main finding is the impossibility to predict the physical activity progression patterns, despite having included sociodemographic, interpersonal, environmental and psychological characteristics in addition to the typical clinical COPD variables. We found a large set of COPD-related, functional characteristics associated with the *Inactive* pattern, in accordance with previous, mainly cross-sectional, literature about the determinants of physical activity levels in COPD (2,4). Also higher education levels, lower social support (living alone, not taking care of grandchildren) and higher depression scores related to being in the *Inactive* pattern, although none of these factors remained in the multivariable model suggesting they were subject to confounding.

Most tellingly, we did not identify any factors that could predict among *Active* patients, the evolution to *Improvers* or *Decliners*. Surprisingly, the presence of severe exacerbations during follow-up did not play any role. It could be speculated that our harmonized exacerbation data was not detailed enough to distinguish the severity of exacerbations, the length of hospital stay or the time from the last exacerbation to physical activity assessment at follow-up. We also considered the role of incident comorbidities during follow-up, which could have influenced behavior, but they were not significantly different for the three patterns. Pharmacological treatment for COPD was not different across progression patterns discarding any potential role for treatment inappropriateness. Moreover, we did not find an association between the recruitment season and physical activity progression. This is in line with the hypothesis that the recruitment season, although possibly affecting the baseline levels of physical activity (12,18,33), would not affect the progression pattern during a follow-up of 12 months. Finally, we did not find an effect of accumulated rainfall on physical activity progression, as recently described cross-sectionally in the same PROactive population (14).

Our study has several implications. It adds to the current knowledge that contrary to the general belief not all patients decline but some patients considerably improve their physical activity, which should be confirmed in future research and shows the importance of including a usual care group in intervention studies. The limitation of traditional clinical COPD characteristics to predict physical activity progression suggests that further research should broaden the view and give more attention to interpersonal and environmental factors potentially related to the individual's motivation. As the optimal timing and use of physical activity interventions to improve physical activity (especially in the long term) is still unclear (34), understanding the different COPD progression patterns may help to overcome a one-size-fits-all approach and customize

physical activity promotion to reflect different physical activity practices and different treatment needs (35). Finally, our results highlight the limitation of using mean population values in phenomena that are heterogeneous in nature.

A major strength of our study is the inclusion of patients across a broad spectrum of disease severities and physical activity in several European cities. ~~making our results applicable to a large COPD population;~~ This makes our results applicable (i.e., more representative) to a larger COPD population than a single recruitment setting or severity group. In addition, the inclusion of patients from diverse geographic locations allowed us to indirectly control for residual confounding. Moreover, we included some variables beyond the conventional clinical COPD characteristics (36). The use of the hypothesis-free clustering approach allowed us to identify patterns of physical activity progression based on the distribution of the data without prior assumptions.

However, we acknowledge some shortcomings. We had a small sample size for some of the hypothesized determinants of physical activity progression patterns, such as dog walking, current pulmonary rehabilitation and knowledge of baseline physical activity, which precluded our ability to test their role. Similarly, we did not collect information on some physical activity barriers (eg costs or transportation difficulties), which precluded testing their role on physical activity progression. The drop-out was 29% which is comparable to previous studies (37,38) but the excluded patients had worse functional parameters, and we cannot rule out that they would have presented with a fourth, potentially declining pattern. The two measurement points available for both studies allowed to investigate only linear patterns over time. Having more data points could provide more detailed information on the trajectories. In addition, a longer follow-up would have been desirable, but the 12-month span appears reasonably long to provide

this first novel insight into physical activity patterns. Finally, one might argue that pooling of the two studies was not appropriate, although our sensitivity analyses showed similar cluster results and characteristics and it resulted in a broad spectrum of physical activity and COPD severity.

In conclusion, the natural change in physical activity over time in COPD patients is heterogeneous and three distinct patterns of physical activity progression have been identified: a predominant *Inactive* pattern, related to worse scores for clinical COPD characteristics, and two *Active* patterns, *Improvers* and *Decliners*, which cannot be predicted at baseline.

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Table 1 Patient characteristics at baseline and at 12-month follow-up for all patients (n=291) and by study group (Urban Training and PROactive study).

	All patients	Urban Training study	PROactive study
	n = 291 (100%)	n = 148[a] (51%)	n = 143[a] (49%)
Sociodemographic			
Age (years)	68±8	69±8	67±8
Sex (men)	237 (81)	130 (88)	107 (75)
Current smoker	52 (18)	30 (20)	22 (15)
Pack-years	58±41	60±45	56±37
Education, high school or higher	168 (58)	49 (33)	119 (83)
Interpersonal			
Living with a partner[b]	216 (74)	124 (84)	92 (65)
Active worker[c]	36 (12)	16 (11)	20 (14)
Grandparenting[d]	67 (45)	67 (45)	-
Dog walking[d]	20 (14)	20 (14)	-
Environmental			
Recruitment season			
Spring	35 (12)	35 (24)	0 (0)
Summer	58 (20)	15 (10)	43 (30)
Fall	154 (53)	54 (36)	100 (70)
Winter	44 (15)	44 (30)	0 (0)
Average rainfall (h/day)[e,f]	0.62 (0.30-1.13)	-	0.62 (0.30-1.13)
Urban vulnerability index (from 0 -lowest to 1 –highest)[d,g]	0.637±0.175	0.637±0.175	-
Clinical			
FEV_1 (% predicted)	58.6±19.3	58.2±17.6	59.0±21.0
FEV_1/FVC ratio	0.51±0.13	0.55±0.12	0.48±0.13
Airflow limitation severity (post-bronchodilator FEV_1)			
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	39 (13)	15 (10)	24 (17)
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	147 (51)	80 (54)	67 (47)
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	88 (30)	45 (30)	43 (30)
GOLD 4: Very Severe ($FEV_1 < 30\%$ predicted)	17 (6)	8 (6)	9 (6)
6MWD (meters)	477±103	501±83	452±116
CAT score (0–40)	12.9±7.6	12.2±7.6	13.6±7.5
CCQ score (0-6)	1.55±0.98	1.40±0.95	1.70±0.98
C-PPAC amount score (0-100)	69.0±15.8	74.7±14.9	63.8±14.9
C-PPAC difficulty score (0-100)	78.4±14.5	82.7±13.4	74.5±14.5
C-PPAC total score (0-100)	73.7±12.8	78.7±11.5	69.2±12.3
mMRC score (0-4)	1.3±0.9	1.1±0.8	1.5±1.0
Any COPD exacerbation with hospital admission in previous 12 months	34 (12)	12 (8)	22 (15)
BMI (kg/m^2)	27.6±4.6	28.3±4.6	26.8±4.6
FFMI (kg/m^2)	19.0±3.0	19.6±3.2	18.4±2.8
Cardiovascular disease[h]	176 (60)	90 (61)	86 (60)
Ischemic heart disease[h]	29 (10)	13 (9)	16 (11)
Diabetes mellitus[h]	51 (18)	38 (26)	13 (9)
LABA or LAMA, alone	41 (14)	23 (16)	18 (13)
Inhaled corticosteroid with LABA and/or LAMA	179 (62)	80 (54)	99 (71)
Pulmonary rehabilitation at baseline	15 (5)	6 (4)	9 (6)
Knowledge of baseline PA	19 (7)	19 (13)	0 (0)
Psychological			
Anxiety (HAD-A, 0-21)	5±4	5±4	5±4
Depression (HAD-D, 0-21)	4±3	3±3	5±3
Physical activity			
Step count (steps/day)	6720±3667	7783±3847	5619±3121

Time in moderate-to-vigorous physical activity (≥3 METs; min/day)	99.4±45.3	109.1±45.7	89.4±42.8
Intensity during walking (m/s^2)	1.86±0.31	1.88±0.32	1.84±0.29
Sedentary time (h/day)	10.53±1.94	10.43±1.48	10.64±2.31
Wearing time (h/day)	14.73±1.56	14.64±0.54	14.81±2.16
Follow-up data			
Any COPD exacerbation with hospital admission during follow-up	28 (10)	10 (7)	18 (13)
Any incident comorbidity during follow-up[d,i]	34 (23)	34 (23)	-
Pulmonary rehabilitation during follow-up	16 (6)	6 (4)	10 (7)
Wearing time at follow-up (h/day)	14.52±1.63	14.60±0.61	14.43±2.24

Notes: Data are presented as n (%), mean±SD or median (interquartile range).
[a]Some variables have missing values, as follows. Urban Training: 1 in education, 25 in C-PPAC scores, 1 in any COPD exacerbation with hospital admission in previous 12 months, 18 in FFMI, 2 in HAD anxiety and depression, 5 in any COPD exacerbation with hospital admission during follow-up, 2 in pulmonary rehabilitation during follow-up; PROactive: 1 in living with a partner, 21 in average rainfall, 1 in CAT score, 1 in CCQ score, 6 in C-PPAC scores, 8 in FFMI, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in pulmonary rehabilitation during follow-up.
[b]marital status: living with a partner vs single, widowed or divorced.
[c]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.
[d]only available for Urban Training.
[e]only available for PROactive.
[f]average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.
[g]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.
[h]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.
[i]incident comorbidities included ICD10 codes C00 to N99.
Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale – Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression; MET: metabolic equivalent of task.

Table 2 Patient characteristics by physical activity progression pattern (*Inactive, Active Improvers* and *Active Decliners*) in 291 COPD patients.

	Inactive	***Active Improvers***	***Active Decliners***	**p-value for *Inactive* vs *Active Improvers* and *Decliners*[b]**	**p-value for *Active Improvers* vs *Decliners*[b]**
	n = 173[a] (59%)	**n = 49[a] (17%)**	**n = 69[a] (24%)**		
Urban Training study	59 (34)	39 (80)	50 (72)		
PROactive study	114 (66)	10 (20)	19 (28)		
Sociodemographic					
Age (years)	68±8	69±9	67±7	0.282	0.079
Sex (men)	137 (79)	41 (84)	59 (86)	0.931	0.789
Current smoker	33 (19)	5 (10)	14 (20)	0.152	0.152
Pack-years	60±38	63±52	49±40	0.187	0.082
Education, high school or higher	124 (72)	20 (42)	24 (35)	**0.006**	0.452
Interpersonal					
Living with a partner[c]	115 (66)	42 (88)	59 (86)	**0.017**	0.714
Active worker[d]	18 (10)	6 (12)	12 (17)	0.088	0.454
Grandparenting[e]	20 (34)	21 (54)	26 (52)	**0.039**	0.863
Environmental					
Average rainfall (h/day)[f,g]	0.63 (0.33-1.13)	0.90 (0.57-1.47)	0.33 (0.23-1.00)	0.877	0.329
Urban vulnerability index (from 0 -lowest to 1 –highest)[e,h]	0.646±0.176	0.613±0.200	0.646±0.153	0.312	0.369
Clinical					
FEV_1 (% predicted)	55.9±19.8	62.9±15.8	62.4±19.5	**0.001**	0.875
FEV_1/FVC ratio	0.48±0.14	0.55±0.11	0.55±0.11	**0.004**	0.904
6MWD (meters)	446±105	521±90	524±78	**<0.001**	0.861
CAT score (0-40)	14.2±7.7	11.5±7.3	10.5±6.6	**0.002**	0.435
CCQ score (0-6)	1.74±0.97	1.23±0.91	1.29±0.93	**0.001**	0.780
C-PPAC difficulty score (0-100)[i]	74.9±14.7	82.6±13.6	84.8±11.6	**<0.001**	0.380
mMRC score (0-4)	1.5±1.0	1.0±0.8	0.9±0.7	**<0.001**	0.329
Any COPD exacerbation with hospital admission in previous 12 months	24 (14)	4 (8)	6 (9)	0.517	0.918
BMI (kg/m^2)	27.6±5.0	27.5±3.9	27.5±4.2	0.139	0.999
FFMI (kg/m^2)	18.9±3.0	19.3±2.9	19.0±3.1	0.650	0.591
Cardiovascular disease[j]	109 (63)	28 (57)	39 (57)	0.221	0.930
Ischemic heart disease[j]	18 (10)	5 (10)	6 (9)	0.898	0.807
Diabetes mellitus[j]	23 (13)	11 (22)	17 (25)	0.412	0.786
LABA or LAMA, alone	24 (14)	7 (14)	10 (15)	0.796	0.949
Inhaled corticosteroid with LABA and/or LAMA	115 (67)	28 (57)	36 (53)	0.311	0.658
Psychological					
Anxiety (HAD-A, 0-21)	5±4	5±3	5±4	0.755	0.774
Depression (HAD-D, 0-21)	5±3	3±3	3±3	**0.009**	0.992
Follow-up data					
Any COPD exacerbation with hospital admission during follow-up	19 (11)	4 (8)	5 (7)	0.759	0.846
Any incident comorbidity during follow-up[e,k]	10 (17)	10 (26)	14 (28)	0.191	0.804

Notes: Data are presented as n (%), mean±SD or median (interquartile range).
[a]Some variables have missing values, as follows. *Inactive*: 15 in average rainfall, 1 in CAT total, 1 in CCQ score, 14 in C-PPAC difficulty score, 17 in FFMI, 2 in LABA or LAMA, alone, 2 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in any COPD exacerbation with hospital admission during follow-up; *Active Improvers*: 1 in education, 1 in living with a partner, 2 in average rainfall, 5 in C-PPAC difficulty score, 4 in FFMI, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up; *Active Decliners*: 4 in average rainfall, 12 in C-PPAC difficulty score, 1 in any COPD exacerbation with hospital admission in previous 12 months, 5 in FFMI, 1 in LABA or LAMA, alone, 1 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up.
[b]p-value from mixed logistic regression models with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).
[c]marital status: living with a partner vs single, widowed or divorced.
[d]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.
[e]only available for Urban Training.
[f]only available for PROactive.
[g]average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.
[h]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.
[i]only C-PPAC difficulty is provided as C-PPAC amount and total score include steps/day which were used for the generation of the PA patterns and therefore cannot be assessed as predictors.
[j]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.
[k]incident comorbidities included ICD10 codes C00 to N99.
Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting beta$_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale - Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression.

Table 3 Adjusted predictive factors for *Inactive* and *Active Improvers* vs *Active Decliners* in 291 COPD patients.

	Active Decliners	***Inactive***		***Active Improvers***	
	RRR (95% CI)	**RRR (95% CI)**	**p-value[a]**	**RRR (95% CI)**	**p-value[a]**
6MWD (per 10m)	1.00 (ref)	0.94 (0.90-0.98)	**0.001**	1.00 (0.96-1.05)	0.868
mMRC score (per 1 point)	1.00 (ref)	1.71 (1.12-2.60)	**0.012**	1.23 (0.73-2.07)	0.437

Notes: [a]p-value from multinomial regression model with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).
Abbreviations: RRR: relative risk ratio; CI: confidence interval. 6MWD: 6-min walking distance; mMRC: modified Medical Research Council.

Figure 1 Physical activity variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*).

Notes: Data are presented as mean±SE (specific numbers are presented in Table S2). * p-value ≤0.05.
Abbreviations: MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent of task.

Figure 2 Physical activity experience variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*).

Notes: Data are presented as mean±SE (specific numbers are presented in Table S2). * p-value ≤0.05.
Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score). C-PPAC variables have 87 missing values: 38 in *Inactive*, 21 in *Active Improvers*, and 28 in *Active Decliners*.

Patterns of physical activity progression in patients with COPD

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Abstract

Introduction: Although mean physical activity in COPD patients declines by 400 to 500 steps/day annually, it is unknown whether the natural progression is the same for all patients. We aimed to identify distinct physical activity progression patterns using a hypothesis-free approach and to assess their determinants.

Methods: We pooled data from two cohorts (usual care arm of Urban Training [NCT01897298] and PROactive initial validation [NCT01388218] studies) measuring physical activity at baseline and 12 months (Dynaport MoveMonitor). We identified clusters (patterns) of physical activity progression (based on levels and changes of steps/day) using k-means, and compared baseline sociodemographic, interpersonal, environmental, clinical and psychological characteristics across patterns.

Results: In 291 COPD patients (mean±SD 68±8 years, 81% male, FEV_1 59±19%$_{pred}$) we identified three distinct physical activity progression patterns: *Inactive* (n=173 [59%], baseline: 4621±1757 steps/day, 12-month change (Δ): -487±1201 steps/day), *Active Improvers* (n=49 [17%], baseline: 7727±3275 steps/day, Δ: +3378±2203 steps/day) and *Active Decliners* (n=69 [24%], baseline: 11267±3009 steps/day, Δ: -2217±2085 steps/day). After adjustment in a mixed multinomial logistic regression model using *Active Decliners* as reference pattern, a lower 6-min walking distance (RRR [95% CI] 0.94 [0.90-0.98] per 10m, p=0.001) and a higher mMRC dyspnea score (1.71 [1.12-2.60] per 1 point, p=0.012) were independently related with being *Inactive.* No baseline variable was independently associated with being an *Active Improver*.

Conclusions: The natural progression in physical activity over time in COPD patients is heterogeneous. While *Inactive* patients relate to worse scores for clinical COPD characteristics, *Active Improvers* and *Decliners* cannot be predicted at baseline.

Keywords

COPD, physical activity, patterns of progression, cluster analysis, determinants

Abbreviations

BMI, body mass index; CAT, COPD assessment test; CCQ, clinical COPD questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; C-PPAC, clinical visit—PROactive physical activity in COPD; FEV1, forced expiratory volume in 1 second; FFMI, fat free mass index; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HAD-A, hospital anxiety and depression scale – anxiety; HAD-D, hospital anxiety and depression scale – depression; LABA: long-acting beta$_2$-agonists; LAMA: long-acting anti-muscarinics; MET, metabolic equivalent of task; mMRC, modified medical research council dyspnea score; 6MWD, 6-min walking distance; MVPA, moderate to vigorous physical activity; RRR, relative risk ratio; SD, standard deviation.

Introduction

Physical activity is a key prognostic factor in chronic obstructive pulmonary disease (COPD), yet poorly understood. COPD patients are less active than healthy controls from the early stages of disease onwards (1–3) and this reduced activity has been associated with impaired prognosis and accelerated progression of COPD (4,5). For this reason, several national and international COPD guidelines recommend encouraging patients to maintain a good physical activity level (6,7).

Despite patients' and health professionals' efforts, physical activity has been shown to exhibit a spontaneous decline of an average of 400 to 500 steps/day per year in COPD patients (8–14). Such observed decline has been related, although not consistently, to lower lung function levels (10,11), the presence of exacerbations (15–17) or the seasonality of testing (eg, decline observed in patients going from summer to winter) (12,18). Given the heterogeneous nature and progression of COPD (19), it can be hypothesized that physical activity progression also displays different patterns, not captured by the mean physical activity values. Two previous studies support this hypothesis by showing distinct physical activity trajectories over 9 months after a pulmonary rehabilitation program (20,21). However, the reported progression in physical activity after rehabilitation programs probably does not reflect how physical activity evolves in the wider COPD population nor in an observational setting, where patients receive a variable combination of pharmacological and non-pharmacological treatments.

We aimed (1) to identify, using a hypothesis-free approach, distinct patterns of natural physical activity progression in COPD patients recruited from diverse settings (primary care, hospital and rehabilitation services) and followed during 12 months; and (2) to

assess the baseline sociodemographic, interpersonal, environmental, clinical and psychological determinants for the identified patterns. Better understanding of the natural progression of physical activity, of potential distinct patterns and of their determinants could help to individualize strategies to increase (or prevent a decline in) physical activity.

Methods

Study design and patient population

This was an observational (no intervention) cohort study of 12-month follow-up including patients from: (1) the usual care arm (n=205) from the Urban Training study (22), that recruited patients from primary care and tertiary hospitals in five Catalan seaside municipalities (Badalona, Barcelona [center and shore areas], Mataró, Viladecans and Gavà); and (2) the clinically stable patients (n=207) from the PROactive validation study (23), that recruited patients from primary care settings, rehabilitation centers and tertiary hospitals in five European cities (Athens/Greece, Edinburgh and London/United Kingdom, Groningen/Netherlands, and Leuven/Belgium). Both studies defined COPD according to ATS/ERS (post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.70) (24). Patients were included in the present analyses if they had a valid physical activity measure (see below) at baseline and 12-month follow-up.

Both studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients.

Physical activity measurements

Physical activity was objectively measured using the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands) (25) for one week at baseline and follow-up. In Urban Training, patients wore the monitor for 24 hours and data during waking hours (from 07:00 h to 22:00 h) were retrieved. In PROactive, patients wore the device during waking hours. A valid physical activity measurement was defined as a minimum of three days with at least 8 hours of wearing time within waking hours for both studies (26); details have been previously published (22,23). A physical activity report was provided to patients if requested.

We used step count as the primary outcome to define physical activity progression patterns, and time spent in physical activity of moderate to vigorous intensity (MVPA, ≥3 METs [metabolic equivalents of tasks] min/day), movement intensity (m/s^2) during walking, and sedentary time (sum of lying and sitting time, hours/day) as secondary physical activity outcomes to describe patterns. Physical activity experience was assessed by the amount, difficulty and total scores of the Clinical visit-PROactive Physical Activity in COPD (C-PPAC) tool (23).

Other measurements

We used variables available from both studies (ie exactly the same or equivalent standardized questions and procedures had been used) or variables that were available from one study only but had been related to physical activity or its evolution in the literature: (i) sociodemographic: age, sex, smoking history and education; (ii) interpersonal: marital status, working status, grandparenting and dog walking; (iii) environmental: season of recruitment, average yearly rainfall and urban vulnerability index (a measure of socioeconomic status at the census tract level); (iv) clinical: post-

bronchodilator FEV_1 and FVC, the 6-min walking distance (6MWD) test, the COPD Assessment test (CAT), the Clinical COPD Questionnaire (CCQ), the modified Medical Research Council dyspnea scale (mMRC), the number of acute COPD exacerbations requiring a hospital admission in the previous 12 months and during follow-up, body mass index (BMI) and fat free mass index (FFMI) by physical examination and bioelectrical impedance, comorbidities from medical records, pharmacological treatment for COPD, pulmonary rehabilitation at baseline and follow-up, incident diseases during follow-up, and knowledge of baseline physical activity (ie report on request); and (v) psychological: the Hospital Anxiety (HAD-A) and Depression (HAD-D) scores. Full details on study procedures and quality control have been reported previously (22,23,27).

Statistical analysis

Sample size calculations, missing data strategy and full statistical analyses are provided in the supplement.

We identified cluster groups (physical activity patterns) using k-means (28), a hypothesis-free method that allowed grouping patients based on the baseline level, the final level and the change in daily step count. To characterize the patterns, we described physical activity and physical activity experience variables according to the cluster groups and compared baseline to follow-up values by paired t-tests.

To assess determinants of physical activity progression patterns, we first compared subjects' characteristics by physical activity patterns and obtained p-values from mixed logistic regression models with random intercepts for study and city area to account for possible heterogeneity in unmeasured characteristics related to study and city area.

Then we built a multivariable multinomial regression model using the generalized linear latent and mixed model, with also random intercepts for study and city (29). Model building combined step-forward and backward algorithms and we tested goodness of fit of the final model.

As sensitivity analyses, we (1) repeated cluster analysis separately for Urban Training and PROactive; (2) tested the association between the change in daily step count and the change in wearing time overall and per pattern; and (3) repeated the clustering after excluding patients included in pulmonary rehabilitation programs at baseline and/or during follow-up.

All analyses were conducted using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

Results

From 412 patients at baseline, 291 (71%) completed the follow-up visit and were included in the current analyses (Figure S1). These patients had a higher proportion of males, better functional status and were more active at baseline than those lost-to follow-up (Table S1). Included patients were 81% male and had a mean age of 68 years, FEV_1 of 59% predicted, 6MWD of 477 m, mMRC dyspnea score of 1.3, and walked 6720 steps/day (Table 1). Compliance with the activity monitor during waking hours was excellent: at baseline median (range) valid days of 7 (3-7) and mean±SD wearing hours of 14.6±0.5 in Urban Training, and 6 (3-7) days and 14.6±0.5 wearing hours in PROactive; and at follow-up, 7 (4-7) days and 14.6±0.6 wearing hours in Urban Training, and 6 (3-7) days and 14.8±2.2 wearing hours in PROactive.

At the group level, the step count did not change over 12 months. In the hypothesis-free approach, we identified three cluster groups (three distinct physical activity patterns) (Figure 1, Table S2). A first cluster (n=173 [59%]), labelled *Inactive* pattern due to the low step count, walked at baseline mean±SD 4621±1757 steps/day and decreased their physical activity by 487±1201 steps/day over 12 months. A second cluster (n=49 [17%]), labelled *Active Improvers*, walked 7727±3275 steps/day at baseline and increased by 3378±2203 steps/day. The third cluster (n=69 [24%]), labelled *Active Decliners*, walked 11267±3009 steps/day at baseline and decreased by 2217±2085 steps/day. Distribution of MVPA and walking intensity by physical activity pattern followed the same sequence as steps/day, except for walking intensity in *Active Improvers* that did not change. Sedentary time did not change for *Inactive*, decreased for *Active Improvers* and increased moderately for *Active Decliners*. The physical activity experience as expressed by C-PPAC scores did not change for the *Inactive* pattern; the *Active Improvers* increased the C-PPAC scores (ie, increased amount and reduced difficulty); the *Active Decliners* decreased the C-PPAC amount and total scores while the C-PPAC difficulty score did not change (Figure 2, Table S2).

Patients in the *Inactive* physical activity pattern had a higher degree of education, a smaller proportion was living with a partner or grandparenting, and they presented with a worse general health status, lower lung function, poorer exercise capacity, worse quality of life and higher dyspnea and depression scores than those in the *Active Improvers* or *Decliners* patterns (Table 2). *Active Improvers* and *Decliners* were very similar in their baseline characteristics, except for their daily step count.

In the multivariable multinomial logistic regression model we used *Active Decliners* as the reference pattern to capture both the determinants of being *Inactive vs Active* and the

determinants of being an *Active Improver vs Decliner*. A lower exercise capacity and a higher mMRC dyspnea score were independently related with being *Inactive* whereas no variable was identified as independently associated with being an *Active Improver* (Table 3). The final model showed good fit. Sensitivity analyses confirmed the results (Tables S3, S4 and S5).

Discussion

This study identified, for the first time to our knowledge, the natural progression of physical activity in COPD patients. We used a hypothesis-free approach that allowed the identification of patterns without *a priori* assumptions about the physical activity changes over time. We found that (1) the natural change in physical activity over time was indeed heterogeneous; (2) the majority of patients (59%) was inactive at baseline and decreased their physical activity level subsequently; (3) among active individuals some increased and some decreased their physical activity level; and (4) although clinical COPD characteristics were related to the physical activity level at baseline they could not predict subsequent physical activity changes.

A first important finding is that physical activity progression in COPD is heterogeneous. In our 12-month study, mean changes in the full group were virtually zero; however when using hypothesis-free clustering methods, we identified one *Inactive* pattern which decreased and two *Active* patterns which increased or decreased physical activity. This observation is in line with previous reports of heterogeneous physical activity progression in patients with rheumatoid arthritis (30). The average lack of 12-month change in step count differs from previous studies that showed overall a decrease in physical activity (8,10,11,13). A potential explanation is that most of these studies recruited patients from outpatient or pulmonary clinics, which may have slightly more

advanced disease and reduced variability in physical activity and COPD characteristics as compared to our sample including also primary care. Supporting this, the group of patients who started with a lower physical activity (59%) was similar in their baseline characteristics to previous studies and also had a comparable mean decrease of around 500 steps/day (10,11). Notably, the low overall dyspnea score may have positively influenced the physical activity level of our study population. A second explanation could lie in the high proportion of male subjects and regional differences in physical activity practice (a cohort of patients included in the Mediterranean region (5) had a baseline physical activity comparable to the Urban Training sample). These characteristics of our sample could justify the two patterns with relatively high baseline physical activity and an average small physical activity change.

The second important finding is that there seems to exist a group of COPD patients (our *Active Improvers*) that spontaneously increase their physical activity over time. Of note, such observed increase of >3000 steps/day is remarkably high given that the minimal important difference has been proposed between 600 and 1100 steps/day (31). There are several possibilities that would explain this observed increase. First, some patients could have been inactive at baseline by chance; however, we tested this option against study records by screening for atypical events and it did not hold true. Second, regression to the mean could account for part of the increase, but in our data regression to the mean was estimated to account for maximal 25% of the effect. Third, changes in daily steps could be due to changes in wearing time, but this was not the case in our study (Table S4). Fourth, patients could have increased their physical activity after participation in rehabilitation programs, but this was dismissed in our analysis (Table S5). Finally, we considered that some patients in the usual care arm of Urban Training could have increased their physical activity due to being enrolled in a physical activity

study. However, the proportion of patients from Urban Training was similar between *Active Improvers* and *Active Decliners*. Thus, we suggest that some patients do actually increase their physical activity.

The evolution of other physical activity variables provided complementary information. Time in MVPA and sedentary time (opposite direction) paralleled the progression of step count in all three patterns, supporting previous research that suggested that in COPD patients, physical activity and sedentary time provide information about the same concept (5). We also investigated the progression of physical activity from the perspective of patients. As expected, C-PPAC amount and total scores followed a trend similar to the objectively measured physical activity, as they include steps/day in their calculation. However, C-PPAC difficulty score remained unchanged in *Inactive* and *Active Decliners* and increased (ie, less difficulty) in *Active Improvers*, suggesting that the observed increase in amount could be related to experiencing fewer difficulties (less dyspnea for instance (32)) while being active.

Our third main finding is the impossibility to predict the physical activity progression patterns, despite having included sociodemographic, interpersonal, environmental and psychological characteristics in addition to the typical clinical COPD variables. We found a large set of COPD-related, functional characteristics associated with the *Inactive* pattern, in accordance with previous, mainly cross-sectional, literature about the determinants of physical activity levels in COPD (2,4). Also higher education levels, lower social support (living alone, not taking care of grandchildren) and higher depression scores related to being in the *Inactive* pattern, although none of these factors remained in the multivariable model suggesting they were subject to confounding.

Most tellingly, we did not identify any factors that could predict among *Active* patients, the evolution to *Improvers* or *Decliners*. Surprisingly, the presence of severe exacerbations during follow-up did not play any role. It could be speculated that our harmonized exacerbation data was not detailed enough to distinguish the severity of exacerbations, the length of hospital stay or the time from the last exacerbation to physical activity assessment at follow-up. We also considered the role of incident comorbidities during follow-up, which could have influenced behavior, but they were not significantly different for the three patterns. Pharmacological treatment for COPD was not different across progression patterns discarding any potential role for treatment inappropriateness. Moreover, we did not find an association between the recruitment season and physical activity progression. This is in line with the hypothesis that the recruitment season, although possibly affecting the baseline levels of physical activity (12,18,33), would not affect the progression pattern during a follow-up of 12 months. Finally, we did not find an effect of accumulated rainfall on physical activity progression, as recently described cross-sectionally in the same PROactive population (14).

Our study has several implications. It adds to the current knowledge that contrary to the general belief not all patients decline but some patients considerably improve their physical activity, which should be confirmed in future research and shows the importance of including a usual care group in intervention studies. The limitation of traditional clinical COPD characteristics to predict physical activity progression suggests that further research should broaden the view and give more attention to interpersonal and environmental factors potentially related to the individual's motivation. As the optimal timing and use of physical activity interventions to improve physical activity (especially in the long term) is still unclear (34), understanding the different COPD progression patterns may help to overcome a one-size-fits-all approach and customize

physical activity promotion to reflect different physical activity practices and different treatment needs (35). Finally, our results highlight the limitation of using mean population values in phenomena that are heterogeneous in nature.

A major strength of our study is the inclusion of patients across a broad spectrum of disease severities and physical activity in several European cities. This makes our results applicable (i.e., more representative) to a larger COPD population than a single recruitment setting or severity group. In addition, the inclusion of patients from diverse geographic locations allowed us to indirectly control for residual confounding. Moreover, we included some variables beyond the conventional clinical COPD characteristics (36). The use of the hypothesis-free clustering approach allowed us to identify patterns of physical activity progression based on the distribution of the data without prior assumptions.

However, we acknowledge some shortcomings. We had a small sample size for some of the hypothesized determinants of physical activity progression patterns, such as dog walking, current pulmonary rehabilitation and knowledge of baseline physical activity, which precluded our ability to test their role. Similarly, we did not collect information on some physical activity barriers (eg costs or transportation difficulties), which precluded testing their role on physical activity progression. The drop-out was 29% which is comparable to previous studies (37,38) but the excluded patients had worse functional parameters, and we cannot rule out that they would have presented with a fourth, potentially declining pattern. The two measurement points available for both studies allowed to investigate only linear patterns over time. Having more data points could provide more detailed information on the trajectories. In addition, a longer follow-up would have been desirable, but the 12-month span appears reasonably long to provide

this first novel insight into physical activity patterns. Finally, one might argue that pooling of the two studies was not appropriate, although our sensitivity analyses showed similar cluster results and characteristics and it resulted in a broad spectrum of physical activity and COPD severity.

In conclusion, the natural change in physical activity over time in COPD patients is heterogeneous and three distinct patterns of physical activity progression have been identified: a predominant *Inactive* pattern, related to worse scores for clinical COPD characteristics, and two *Active* patterns, *Improvers* and *Decliners*, which cannot be predicted at baseline.

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Table 1 Patient characteristics at baseline and at 12-month follow-up for all patients (n=291) and by study group (Urban Training and PROactive study).

	All patients	Urban Training study	PROactive study
	n = 291 (100%)	n = 148[a] (51%)	n = 143[a] (49%)
Sociodemographic			
Age (years)	68±8	69±8	67±8
Sex (men)	237 (81)	130 (88)	107 (75)
Current smoker	52 (18)	30 (20)	22 (15)
Pack-years	58±41	60±45	56±37
Education, high school or higher	168 (58)	49 (33)	119 (83)
Interpersonal			
Living with a partner[b]	216 (74)	124 (84)	92 (65)
Active worker[c]	36 (12)	16 (11)	20 (14)
Grandparenting[d]	67 (45)	67 (45)	-
Dog walking[d]	20 (14)	20 (14)	-
Environmental			
Recruitment season			
Spring	35 (12)	35 (24)	0 (0)
Summer	58 (20)	15 (10)	43 (30)
Fall	154 (53)	54 (36)	100 (70)
Winter	44 (15)	44 (30)	0 (0)
Average rainfall (h/day)[e,f]	0.62 (0.30-1.13)	-	0.62 (0.30-1.13)
Urban vulnerability index (from 0 -lowest to 1 –highest)[d,g]	0.637±0.175	0.637±0.175	-
Clinical			
FEV_1 (% predicted)	58.6±19.3	58.2±17.6	59.0±21.0
FEV_1/FVC ratio	0.51±0.13	0.55±0.12	0.48±0.13
Airflow limitation severity (post-bronchodilator FEV_1)			
GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted)	39 (13)	15 (10)	24 (17)
GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted)	147 (51)	80 (54)	67 (47)
GOLD 3: Severe ($30\% \leq FEV_1 < 50\%$ predicted)	88 (30)	45 (30)	43 (30)
GOLD 4: Very Severe ($FEV_1 < 30\%$ predicted)	17 (6)	8 (6)	9 (6)
6MWD (meters)	477±103	501±83	452±116
CAT score (0–40)	12.9±7.6	12.2±7.6	13.6±7.5
CCQ score (0-6)	1.55±0.98	1.40±0.95	1.70±0.98
C-PPAC amount score (0-100)	69.0±15.8	74.7±14.9	63.8±14.9
C-PPAC difficulty score (0-100)	78.4±14.5	82.7±13.4	74.5±14.5
C-PPAC total score (0-100)	73.7±12.8	78.7±11.5	69.2±12.3
mMRC score (0-4)	1.3±0.9	1.1±0.8	1.5±1.0
Any COPD exacerbation with hospital admission in previous 12 months	34 (12)	12 (8)	22 (15)
BMI (kg/m^2)	27.6±4.6	28.3±4.6	26.8±4.6
FFMI (kg/m^2)	19.0±3.0	19.6±3.2	18.4±2.8
Cardiovascular disease[h]	176 (60)	90 (61)	86 (60)
Ischemic heart disease[h]	29 (10)	13 (9)	16 (11)
Diabetes mellitus[h]	51 (18)	38 (26)	13 (9)
LABA or LAMA, alone	41 (14)	23 (16)	18 (13)
Inhaled corticosteroid with LABA and/or LAMA	179 (62)	80 (54)	99 (71)
Pulmonary rehabilitation at baseline	15 (5)	6 (4)	9 (6)
Knowledge of baseline PA	19 (7)	19 (13)	0 (0)
Psychological			
Anxiety (HAD-A, 0-21)	5±4	5±4	5±4
Depression (HAD-D, 0-21)	4±3	3±3	5±3
Physical activity			
Step count (steps/day)	6720±3667	7783±3847	5619±3121

Time in moderate-to-vigorous physical activity (≥3 METs; min/day)	99.4±45.3	109.1±45.7	89.4±42.8
Intensity during walking (m/s^2)	1.86±0.31	1.88±0.32	1.84±0.29
Sedentary time (h/day)	10.53±1.94	10.43±1.48	10.64±2.31
Wearing time (h/day)	14.73±1.56	14.64±0.54	14.81±2.16
Follow-up data			
Any COPD exacerbation with hospital admission during follow-up	28 (10)	10 (7)	18 (13)
Any incident comorbidity during follow-up[d,i]	34 (23)	34 (23)	-
Pulmonary rehabilitation during follow-up	16 (6)	6 (4)	10 (7)
Wearing time at follow-up (h/day)	14.52±1.63	14.60±0.61	14.43±2.24

Notes: Data are presented as n (%), mean±SD or median (interquartile range).

[a]Some variables have missing values, as follows. Urban Training: 1 in education, 25 in C-PPAC scores, 1 in any COPD exacerbation with hospital admission in previous 12 months, 18 in FFMI, 2 in HAD anxiety and depression, 5 in any COPD exacerbation with hospital admission during follow-up, 2 in pulmonary rehabilitation during follow-up; PROactive: 1 in living with a partner, 21 in average rainfall, 1 in CAT score, 1 in CCQ score, 6 in C-PPAC scores, 8 in FFMI, 3 in LABA or LAMA, alone, 3 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in pulmonary rehabilitation during follow-up.

[b]marital status: living with a partner vs single, widowed or divorced.

[c]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.

[d]only available for Urban Training.

[e]only available for PROactive.

[f]average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.

[g]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.

[h]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.

[i]incident comorbidities included ICD10 codes C00 to N99.

Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale – Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression; MET: metabolic equivalent of task.

Table 2 Patient characteristics by physical activity progression pattern (*Inactive, Active Improvers* and *Active Decliners*) in 291 COPD patients.

	Inactive	***Active Improvers***	***Active Decliners***	**p-value for *Inactive* vs *Active Improvers* and *Decliners*[b]**	**p-value for *Active Improvers* vs *Decliners*[b]**
	n = 173[a] (59%)	**n = 49[a] (17%)**	**n = 69[a] (24%)**		
Urban Training study	59 (34)	39 (80)	50 (72)		
PROactive study	114 (66)	10 (20)	19 (28)		
Sociodemographic					
Age (years)	68±8	69±9	67±7	0.282	0.079
Sex (men)	137 (79)	41 (84)	59 (86)	0.931	0.789
Current smoker	33 (19)	5 (10)	14 (20)	0.152	0.152
Pack-years	60±38	63±52	49±40	0.187	0.082
Education, high school or higher	124 (72)	20 (42)	24 (35)	**0.006**	0.452
Interpersonal					
Living with a partner[c]	115 (66)	42 (88)	59 (86)	**0.017**	0.714
Active worker[d]	18 (10)	6 (12)	12 (17)	0.088	0.454
Grandparenting[e]	20 (34)	21 (54)	26 (52)	**0.039**	0.863
Environmental					
Average rainfall (h/day)[f,g]	0.63 (0.33-1.13)	0.90 (0.57-1.47)	0.33 (0.23-1.00)	0.877	0.329
Urban vulnerability index (from 0 -lowest to 1 –highest)[e,h]	0.646±0.176	0.613±0.200	0.646±0.153	0.312	0.369
Clinical					
FEV_1 (% predicted)	55.9±19.8	62.9±15.8	62.4±19.5	**0.001**	0.875
FEV_1/FVC ratio	0.48±0.14	0.55±0.11	0.55±0.11	**0.004**	0.904
6MWD (meters)	446±105	521±90	524±78	**<0.001**	0.861
CAT score (0-40)	14.2±7.7	11.5±7.3	10.5±6.6	**0.002**	0.435
CCQ score (0-6)	1.74±0.97	1.23±0.91	1.29±0.93	**0.001**	0.780
C-PPAC difficulty score (0-100)[i]	74.9±14.7	82.6±13.6	84.8±11.6	**<0.001**	0.380
mMRC score (0-4)	1.5±1.0	1.0±0.8	0.9±0.7	**<0.001**	0.329
Any COPD exacerbation with hospital admission in previous 12 months	24 (14)	4 (8)	6 (9)	0.517	0.918
BMI (kg/m^2)	27.6±5.0	27.5±3.9	27.5±4.2	0.139	0.999
FFMI (kg/m^2)	18.9±3.0	19.3±2.9	19.0±3.1	0.650	0.591
Cardiovascular disease[j]	109 (63)	28 (57)	39 (57)	0.221	0.930
Ischemic heart disease[j]	18 (10)	5 (10)	6 (9)	0.898	0.807
Diabetes mellitus[j]	23 (13)	11 (22)	17 (25)	0.412	0.786
LABA or LAMA, alone	24 (14)	7 (14)	10 (15)	0.796	0.949
Inhaled corticosteroid with LABA and/or LAMA	115 (67)	28 (57)	36 (53)	0.311	0.658
Psychological					
Anxiety (HAD-A, 0-21)	5±4	5±3	5±4	0.755	0.774
Depression (HAD-D, 0-21)	5±3	3±3	3±3	**0.009**	0.992
Follow-up data					
Any COPD exacerbation with hospital admission during follow-up	19 (11)	4 (8)	5 (7)	0.759	0.846
Any incident comorbidity during follow-up[e,k]	10 (17)	10 (26)	14 (28)	0.191	0.804

Notes: Data are presented as n (%), mean±SD or median (interquartile range).
[a]Some variables have missing values, as follows. *Inactive*: 15 in average rainfall, 1 in CAT total, 1 in CCQ score, 14 in C-PPAC difficulty score, 17 in FFMI, 2 in LABA or LAMA, alone, 2 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 3 in any COPD exacerbation with hospital admission during follow-up; *Active Improvers*: 1 in education, 1 in living with a partner, 2 in average rainfall, 5 in C-PPAC difficulty score, 4 in FFMI, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up; *Active Decliners*: 4 in average rainfall, 12 in C-PPAC difficulty score, 1 in any COPD exacerbation with hospital admission in previous 12 months, 5 in FFMI, 1 in LABA or LAMA, alone, 1 in inhaled corticosteroid with LABA and/or LAMA, 1 in HAD anxiety and depression, 1 in any COPD exacerbation with hospital admission during follow-up.
[b]p-value from mixed logistic regression models with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).
[c]marital status: living with a partner vs single, widowed or divorced.
[d]working status: active worker (working full-time or part-time) vs. unemployed, housework or retired.
[e]only available for Urban Training.
[f]only available for PROactive.
[g]average rainfall was calculated as the mean of the measurements at baseline, 6 and 12 months.
[h]The urban vulnerability index is a measure of socioeconomic status at the census tract level that combines demographic, economic, residential and subjective indicators, and ranges from lowest [0] to highest [1] level of neighborhood vulnerability.
[i]only C-PPAC difficulty is provided as C-PPAC amount and total score include steps/day which were used for the generation of the PA patterns and therefore cannot be assessed as predictors.
[j]ICD10 codes: I00 to I99 for cardiovascular diseases; I20 to I25 for ischemic heart disease, E14 for diabetes mellitus.
[k]incident comorbidities included ICD10 codes C00 to N99.
Abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; 6MWD: 6-min walking distance; CAT: COPD Assessment Test; CCQ: Clinical COPD Questionnaire; C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score); mMRC: modified Medical Research Council; BMI: body mass index; FFMI: fat free mass index; LABA: long-acting $beta_2$-agonists; LAMA: long-acting anti-muscarinics; HAD-A: Hospital Anxiety and Depression scale - Anxiety; HAD-D: Hospital Anxiety and Depression scale – Depression.

Table 3 Adjusted predictive factors for *Inactive* and *Active Improvers* vs *Active Decliners* in 291 COPD patients.

	Active Decliners	***Inactive***		***Active Improvers***	
	RRR (95% CI)	**RRR (95% CI)**	**p-value**[a]	**RRR (95% CI)**	**p-value**[a]
6MWD (per 10m)	1.00 (ref)	0.94 (0.90-0.98)	**0.001**	1.00 (0.96-1.05)	0.868
mMRC score (per 1 point)	1.00 (ref)	1.71 (1.12-2.60)	**0.012**	1.23 (0.73-2.07)	0.437

Notes: [a]p-value from multinomial regression model with random effects for study (UT and PROactive) and city area (Badalona, Barcelona-center, Barcelona-shore, Mataró, Viladecans/Gavà, Athens, Edinburgh, Groningen, Leuven, London).
Abbreviations: RRR: relative risk ratio; CI: confidence interval. 6MWD: 6-min walking distance; mMRC: modified Medical Research Council.

Figure 1 Physical activity variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*).

Notes: Data are presented as mean±SE (specific numbers are presented in Table S2). * p-value ≤0.05.
Abbreviations: MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent of task.

Figure 2 Physical activity experience variables at baseline and at 12-month follow-up, overall and by PA progression pattern (*Inactive*, *Active Improvers* and *Active Decliners*).

Notes: Data are presented as mean±SE (specific numbers are presented in Table S2). * p-value ≤0.05.
Abbreviations: C-PPAC: Clinical visit—PROactive Physical Activity in COPD (higher numbers indicate a better score). C-PPAC variables have 87 missing values: 38 in *Inactive*, 21 in *Active Improvers*, and 28 in *Active Decliners*.

Figura (Figure)

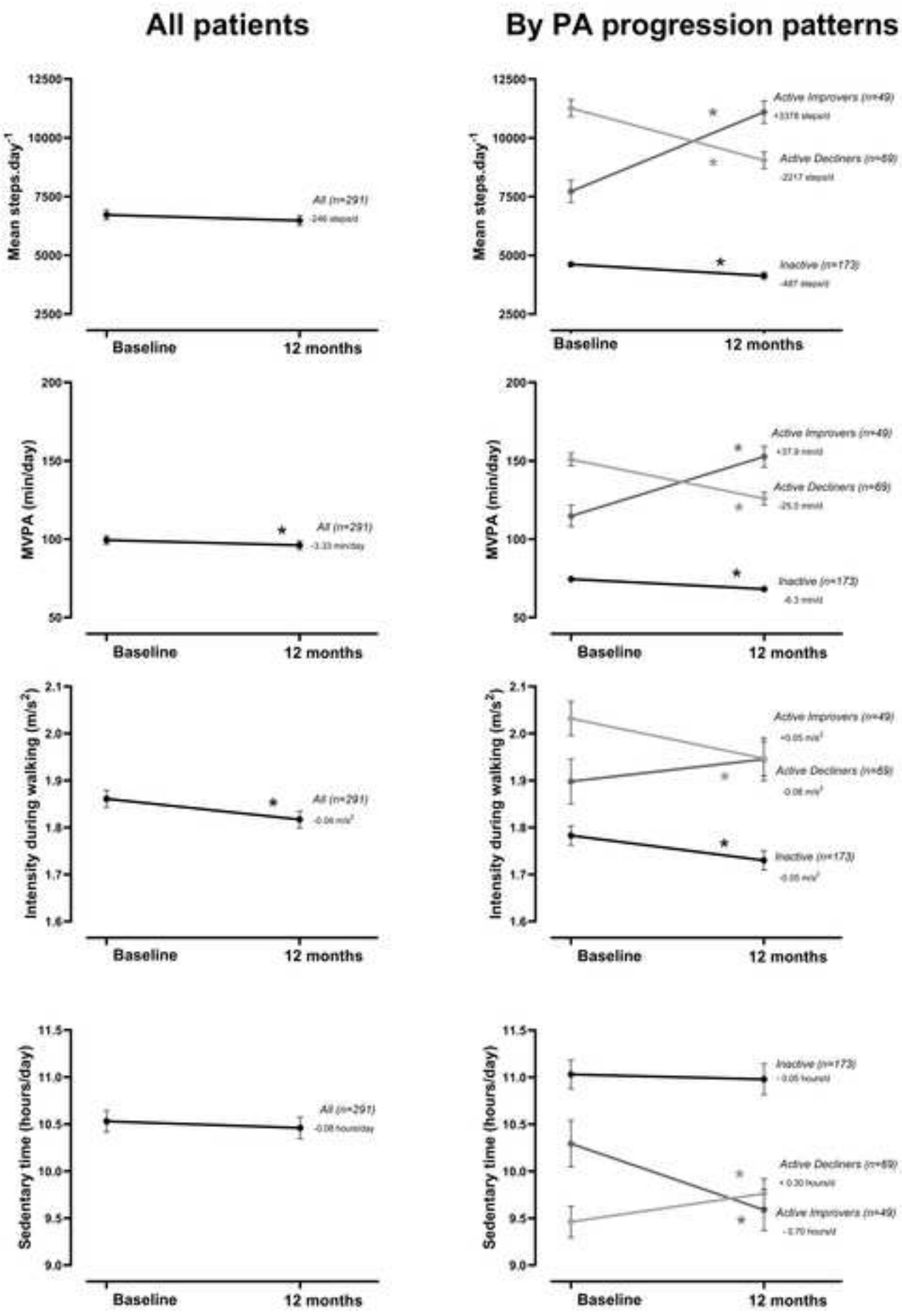
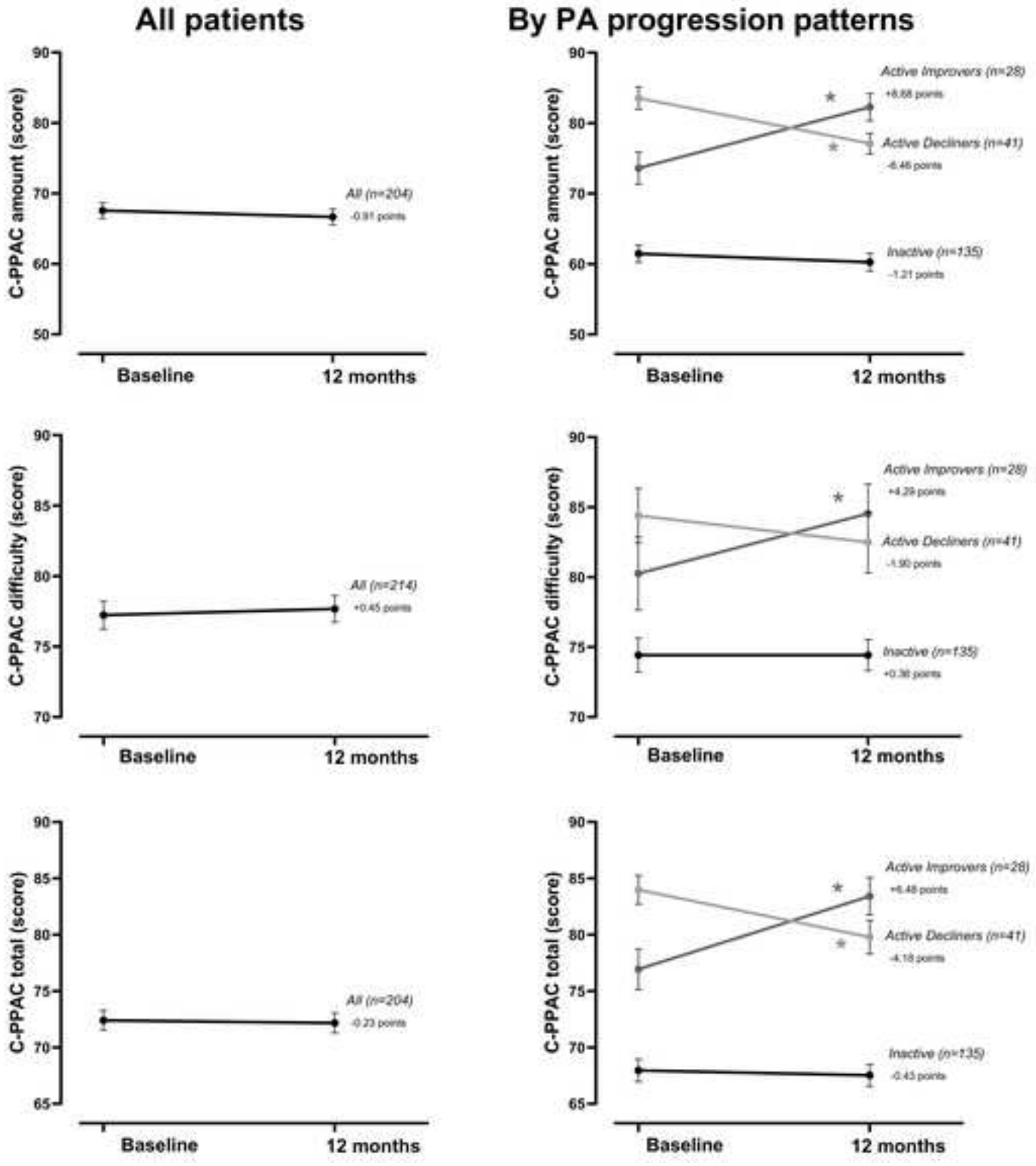


Figura (Figure)



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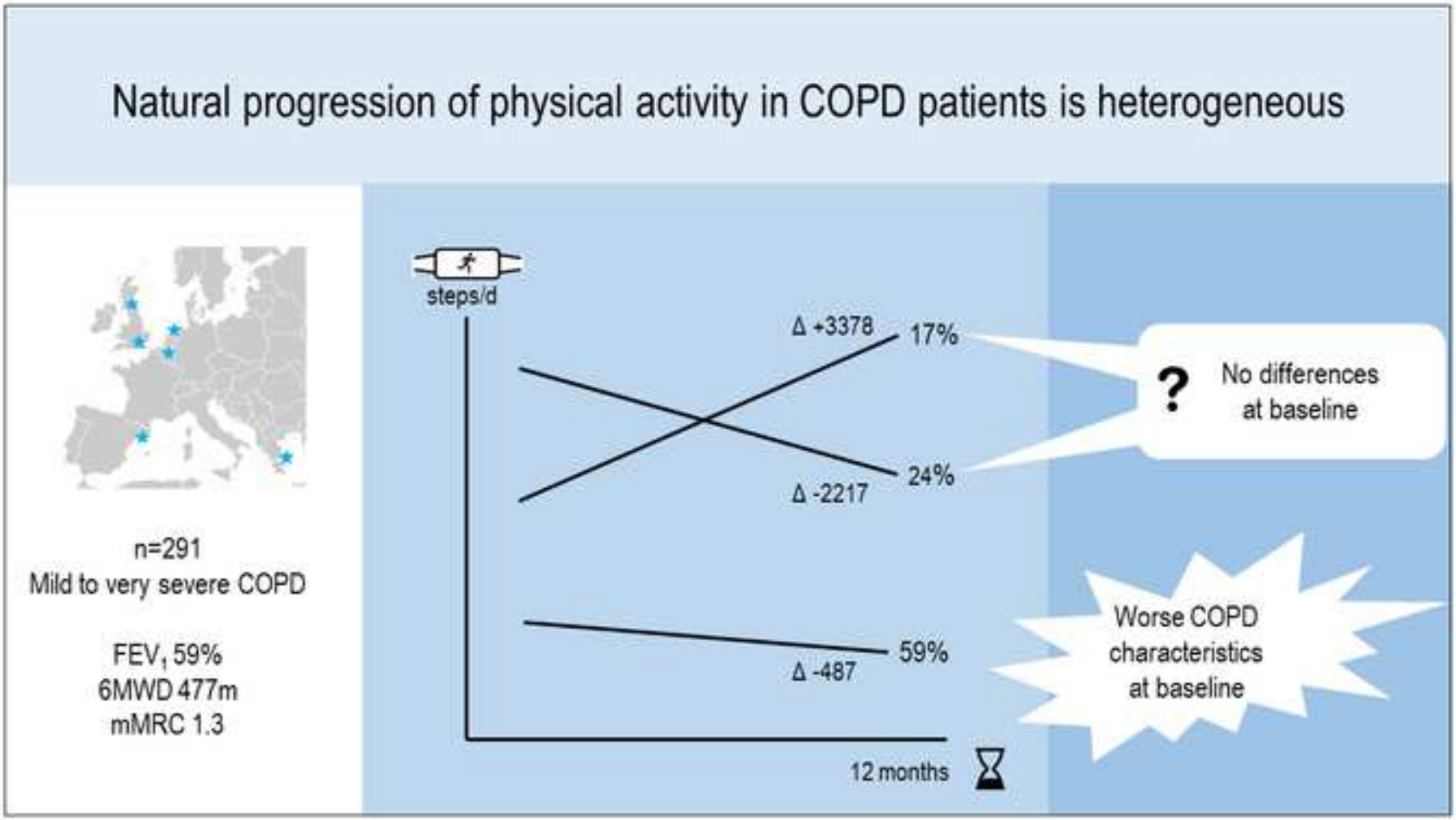

Ethics in publishing

1. Does your research involve experimentation on animals?:
No

2. Does your study include human subjects?:
Yes

- If yes; please provide name of the ethical committee approving these experiments.:
This study was conducted in accordance with the amended Declaration of Helsinki. Both studies were approved by all local institutional review boards and written informed consent, including re-use of data for COPD-related research, was obtained from all patients. The Urban Training trial was approved by the ethics committees of all participating institutions (Comitè Ètic d'Investigació Clínica Parc de Salut MAR 2011/4291/I, Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol i Gurina P11/116, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge PR197/11, Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Germans Trias i Pujol AC-12-004, Comitè Ètic d'Investigació Clínica de l'Hospital Clínic de Barcelona 2011/7061, Comitè Ètic d'Investigació Clínica de l'Hospital de Mataró November 23rd, 2011). The PROactive study was advised and approved by the PROactive ethics and patient advisory boards, and approved by the local ethics committee at each centre (Commissie medische ethiek van de universitaire ziekenhuizen KU Leuven (Leuven, S-55919); Medische ethische toetsingscommissie universitair medisch centrum Groningen (Groningen, Metc 2013.362); RES Committee London—South East (London and Edinburgh, 13/LO/1660); Scientific Council of the 'Sotiria' General Hospital for Chest Diseases (Athens, 27852/7-10-13); Kantonale Ethikkommission Zürich and Ethikkommission Nordwest- und Zentralschweiz (Zurich, KEK-ZH-Nr. 2013-0469).
- If yes; please confirm authors compliance with all relevant ethical regulations. :
Yes
- If yes; please confirm that written consent has been obtained from all patients. :
Yes

3. Does your study include a clinical trial?:
No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:
Yes