**Cluster analysis of physical activity in chronic obstructive pulmonary disease: a multicenter study**

**Corresponding author:**

Rafael Mesquita, MSc, PT

Department of Research & Education, CIRO+, center of expertise for chronic organ failure+; Hornerheide 1, 6085 NM, Horn, The Netherlands; Telephone number: +31 475 587 645; Email: rafaelmesquita14@ymail.com

Rafael Mesquita1,2,\*, Gabriele Spina3,4,\*, Fabio Pitta5, David Donaire-Gonzalez6,7, Brenda M. Deering8, Mehul S. Patel9, Katy E. Mitchell10, Jennifer Alison11,12, Arnoldus J. R. van Gestel13, Stefanie Zogg14, Philippe Gagnon15, Beatriz Abascal-Bolado16,17, Barbara Vagaggini18, Judith Garcia-Aymerich6,7,19, Sue C. Jenkins20, Elisabeth A. P. M. Romme21, Samantha S. C. Kon9, Paul S. Albert22, Benjamin Waschki23, Dinesh Shrikrishna9, Sally J. Singh10, Nicholas S. Hopkinson9, David Miedinger14, Roberto P. Benzo17, François Maltais15, Pierluigi Paggiaro18, Zoe J. McKeough11, Michael I. Polkey9, Kylie Hill20, William D-C. Man9, Christian F. Clarenbach13, Nidia A. Hernandes5, Daniela Savi24, Sally Wootton11, Karina C. Furlanetto5, Li W. Cindy Ng20, Anouk W. Vaes1, Christine Jenkins25, Peter R. Eastwood26, Diana Jarreta27, Anne Kirsten23, Dina Brooks28, David R. Hillman26, Thaís Sant’Anna5, Kenneth Meijer29, Selina Dürr14, Erica P. A. Rutten1, Malcolm Kohler13, Vanessa S. Probst5,30, Ruth Tal-Singer31, Esther Garcia Gil27, Albertus C. den Brinker4, Jörg D. Leuppi14, Peter M. A. Calverley22, Frank W. J. M. Smeenk21, Richard W. Costello8, Marco Gramm23, Roger Goldstein28, Miriam T. J. Groenen1, Helgo Magnussen23, Emiel F. M. Wouters1,2, Richard L. ZuWallack32, Oliver Amft3,33,†, Henrik Watz23,†, Martijn A. Spruit1,34,†.

\*Joint first authors

†Joint senior authors

**Affiliations:**

1Department of Research & Education, Center of expertise for chronic organ failure + (CIRO+), Horn, The Netherlands.

2Department of Respiratory Medicine, Maastricht University Medical Center+ (MUMC+), Maastricht, The Netherlands.

3Department of Signal Processing Systems, Technische Universiteit Eindhoven, Eindhoven, The Netherlands.

4Smart Sensing and Analysis Group, Philips Research, Eindhoven, The Netherlands.

5Laboratory of Research in Respiratory Physiotherapy, Department of Physiotherapy, State University of Londrina (UEL), Londrina, Brazil.

6Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

7CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.

8Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland.

9NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust and Imperial College, London, United Kingdom.

10NIHR EM CLAHRC - Centre for Exercise and Rehabilitation Science, University Hospitals, Leicester, United Kingdom.

11Clinical and Rehabilitation Sciences, The University of Sydney, Sydney, NSW, Australia.

12Physiotherapy Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

13Pulmonary Division, University Hospital of Zurich, Zurich, Switzerland.

14Medical University Clinic, Cantonal Hospital Baselland, Liestal and Medical Faculty, University of Basel, Basel, Switzerland.

15Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Ste-Foy Québec, Université Laval, Québec G1V 4G5, Canada.

16Division of Pulmonary, Hospital U. Marqués de Valdecilla, IFIMAV, Santander, Spain.

17Mindful Breathing Laboratory, Mayo Clinic, Rochester, MN, United States of America.

18Cardio-Thoracic and Vascular Department, University of Pisa, Pisa, Italy.

19Universitat Pompeu Fabra (UPF), Barcelona, Spain.

20School of Physiotherapy and Exercise Science, Curtin University, Perth, WA, Australia.

21Department of Respiratory Medicine, Catharina Hospital, Eindhoven, The Netherlands.

22School of Ageing and Chronic Disease, University Hospital Aintree, Liverpool, United Kingdom.

23Pulmonary Research Institute at LungClinic Grosshansdorf, Airway Research Center North, Member of the German Centre for Lung Research, Grosshansdorf, Germany.

24Department of Pediatrics and Pediatric Neurology, Cystic Fibrosis Center, Sapienza University of Rome, Rome, Italy.

25Woolcock Institute of Medical Research, The University of Sydney, Camperdown, NSW, Australia.

26Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Perth, WA, Australia.

27R&D Centre, Almirall, Barcelona, Spain.

28Respiratory Medicine, West Park Healthcare Centre and Faculty of Medicine, University of Toronto, Toronto, Canada.

29Department of Human Movement Science, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands.

30Center for Research in Health Sciences, University North of Paraná (UNOPAR), Londrina, Brazil.

31GlaxoSmithKline R&D, King of Prussia, PA, United States of America.

32Department of Pulmonary and Critical Care, Saint Francis Hospital and Medical Center, Hartford, CT, United States of America.

33ACTLab group, Chair of Sensor Technology, University Passau, Passau, Germany.

34REVAL - Rehabilitation Research Center, BIOMED - Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium.

**Running title:** Cluster analysis of physical activity in COPD.

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**What is the key question?**

Are physical activity (PA) measures in patients with chronic obstructive pulmonary disease (COPD) different after stratification for clinical characteristic, comparable with those of healthy subjects, and able to identify clusters of patients with distinct characteristics?

**What is the bottom line?**

In COPD patients, PA measures were found to vary considerably depending on the clinical characteristic, to be reduced in comparison with healthy subjects, and to be able to identify five clusters of patients, each with distinct PA measures and clinical characteristics.

**Why read on?**

The present data suggest that outcome measures need to be clearly delineated when evaluating interventions aiming to promote PA in patients with COPD.

**Abstract**

**Background** Physical activity (PA) in patients with chronic obstructive pulmonary disease (COPD) is insufficiently understood.

**Aims** To describe PA measures and hourly patterns in patients with COPD after stratification for clinical characteristics; to compare these measures and patterns between patients and healthy subjects; and to identify clusters of patients based on PA measures.

**Methods** 1001 patients with COPD (65% men; age, 67 years; FEV1, 49% predicted) and 66 healthy subjects (45% men; age, 65 years; FEV1, 107% predicted) were cross-sectionally studied. Daily PA measures and PA hourly patterns (i.e., the graphic representation of the mean intensity per hour during a day) were analyzed based on data from a multi-sensor armband. Principal component analysis (PCA) and cluster analysis were applied to PA data to identify subgroups.

**Results** Age, body mass index (BMI), dyspnea grade and the ADO index (including age, dyspnea, and airflow obstruction) were associated with PA measures and hourly patterns in patients with COPD. Compared to healthy subjects, patients had lower intensities of PA across hourly patterns. Five clusters were identified based on 3 components from the PCA, which accounted for 60% of variance. Importantly, cluster 1 - the most inactive cluster - was characterized by higher BMI, lower FEV1, worse dyspnea and higher ADO index compared to other clusters (*P*<0.05 for all).

**Conclusions** Daily PA measures and hourly patterns in COPD are heterogeneous. Subgroups of patients could be identified based on PA data. These findings may be useful for interventions aiming to promote PA in COPD.

**INTRODUCTION**

Patients with chronic obstructive pulmonary disease (COPD) undertake less physical activity (PA) compared to healthy individuals ([1-3](#_ENREF_1)), and this relative inactivity is related to a higher risk of hospital admission and mortality ([4-8](#_ENREF_4)). Since PA measures can be used as an outcome measure for clinical trials, a greater understanding of the clinical importance of physical activity and inactivity in COPD is needed(REFStatement).

To date, most studies investigating PA in patients with COPD have focused on the average daily value and its standard deviation ([9-14](#_ENREF_9)). Donaire-Gonzalez and colleagues ([15](#_ENREF_15)) were the first to perform more detailed analyses, showing that patients with COPD perform bouts of moderate-to-vigorous PA, and that the frequency of these bouts is inversely associated with the degree of airflow limitation. Nonetheless, a better insight into daily PA of patients with COPD can be achieved by using more detailed analyses, such as daily PA hourly patterns (18, 19) and cluster analysis of PA measures (18, 20-22). Plotting PA hourly provides a graphic representation of the average PA intensity per hour over the course of a day (19, 22, 23). Cluster analysis may be useful to identify subgroups of patients with similar PA characteristics (24), which may assist in targeting therapeutic strategies, and this seems particularly important as interventions thus far have failed to demonstrate important increases in PA in patients with COPD (REFDeering2011;Cindy Ng2012;Steele2008).

PA hourly patterns and cluster analysis of PA measures have not been investigated in a large-scale study in patients with COPD. We hypothesize that distinct PA measures and hourly patterns can be found in patients with different clinical characteristics or in comparison with healthy subjects, and that patients can be clustered into subgroups that associate with clinical characteristics. Therefore, we aimed to i) describe PA measures and hourly patterns in patients with COPD after stratification for clinical characteristics, ii) compare PA measures and hourly patterns between patients with COPD and healthy subjects matched for gender, age and body mass index (BMI) and iii) identify clusters of patients with COPD based on PA measures with the goal of comparing clinical characteristics, PA measures and PA hourly patterns amongst these clusters.

**METHODS**

**Study design and participants**

In this multicenter, post-hoc cross-sectional study, objectively assessed PA data from the United Kingdom, Ireland, the Netherlands, Germany, Switzerland, Italy, Spain, the United States of America, Brazil, and Australia was analyzed; dPublished and/or unpublished PA data (with no overlapping analyses) as assessed by the SenseWear Armband or SenseWear Mini Armband activity monitors (both from BodyMedia Inc., Pittsburgh, PA, USA) was considered for the current analyses. Subjects were included if they met the following inclusion criteria: COPD with a post-bronchodilator forced expiratory volume in the first 1 second (FEV1) / forced vital capacity (FVC) ratio <0.70 (25), stable condition (i.e., no recent exacerbation), and complete data for age, gender, BMI and daily PA measures (see *Assessments* section). Centers from the Netherlands and the UK also provided data on healthy elderly subjects, who were then pairwise-matched (1:1) for gender, age and BMI with a subgroup of patients with COPD. Ethics Board approval was obtained from the local ethics committees, and written informed consent was provided by participants, except for the data from Italy (n=23), which was obtained as part of routine clinical assessments.

**Assessments**

Demographics, anthropometrics, lung function, and clinical data were assessed; details can be found in the online supplement. The SenseWear Armband and SenseWear Mini Armband activity monitors were used to assess PA. Previous studies have described these devices in details and showed their validity both in field (26, 27) and in laboratory studies (28-30). The following thresholds proposed by the American College of Sports Medicine (ACSM) (31) were used to classify the intensity of activities: very light intensity, <2.0 metabolic equivalents of task (MET); light intensity, 2.0 to 2.9 METs; and moderate-to-vigorous intensity, ≥3.0 METs.

A minimum of 4 days (2 weekdays + Saturday + Sunday) was considered acceptable ([9](#_ENREF_9)), with the device being used for ≥22 hours·day-1 (32). Since PA measures during the week and the weekend are known to be different ([9](#_ENREF_9)), only recordings during waking hours and weekdays were considered for the cluster analysis, in order to reduce the variability of the data. Details on the selection of waking hour recordings can be found online. The PA measures, which represent the average of all valid weekdays, were stratified according to different criteria in order to generate distinct variables that could be used for clustering of patients (Table E1, online supplement). Weekend days were used only for the presentation of daily PA hourly patterns, which consist of a graphic representation of the intensity of PA per hour during the course of a day (18, 19, 22, 23).

**Statistical Analysis**

Continuous variables were expressed as median (interquartile range), as most variables presented non-normal distribution. Categorical variables were expressed as absolute and/or relative frequency. Mann-Whitney U test or Kruskal-Wallis test (post hoc Dunn) was used for comparing continuous variables, whilst the chi-square test was used for categorical variables. Spearman coefficient was used to investigate correlations, when appropriate. *P*<0.05 was considered significant and all statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, Illinois, USA) or GraphPad Prism 5 (GraphPad Software, La Jolla, California, USA). Details about sample size calculation can be found in the online supplement.

Cluster analysis was adopted to identify subgroups with distinct PA profiles. Firstly, Principal Component Analysis (PCA) was used to reduce the high-dimensional feature set (180 dimensions) to a lower subspace useful for data visualization (3 dimensions). Secondly, a k-means clustering algorithm with automatic selection of the number of clusters was applied to the 3 dimensional principal components space to separate the subjects into groups with distinct characteristics. The algorithm selects the number of clusters in a way that the corresponding clustering results are the most stable under small perturbations of the input dataset (33). The normalized mean over pairwise clustering distances was used as an instability measure (33). The features were first standardized using z-scores. Feature extraction, PCA and cluster analysis were performed using Matlab R2012b (Mathworks Inc., USA).

**RESULTS**

**General characteristics**

In total, 1001 patients with COPD were analyzed (Table 1). The number of subjects recruited from each country can be found online (Table E2). The majority of the patients were men, had normal-to-overweight BMI and moderate-to-severe degree of airflow limitation, were categorized to GOLD group D (i.e., high risk and more symptoms), and only a small proportion used LTOT.

**Table 1** General characteristics of patients with COPD (n=1001)

|  |  |
| --- | --- |
| **Characteristic** | **Value** |
| Age, yrs | 67 (61 – 72) |
| Male, % | 65 |
| Weight, kg | 74 (62 – 87) |
| Height, m | 1.70 (1.63 – 1.75) |
| BMI, kg·m-2 | 25.8 (22.5 – 29.6) |
| BMI classification, %  Underweight  Normal weight  Overweight  Obese | 7  37  34  22 |
| mMRC dyspnea grade\* | 2 (1 – 3) |
| Long-term oxygen therapy, %† | 10 |
| FEV1, L | 1.31 (0.91 – 1.79) |
| FEV1, % predicted | 49 (34 – 64) |
| FEV1/FVC, % | 45 (35 – 56) |
| DLCO, % predicted‡ | 51 (37 – 67) |
| ADO index\* | 4 (3 – 5) |
| GOLD 2007 classification 1 / 2 / 3 / 4, % | 9 / 40 / 34 / 17 |
| GOLD 2011 classification A / B / C / D, %\* | 29 / 16 / 17 / 38 |

Data expressed as absolute/relative frequency, or median (interquartile range). BMI: body mass index; mMRC: modified Medical Research Council; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide; ADO: age dyspnea obstruction index; GOLD: Global Initiative for Chronic Obstructive Lung Disease. \*Data available for 868 subjects; †Data available for 707 subjects; ‡Data available for 505 subjects.

**Daily PA measures and PA hourly patterns**

The median number of valid days was 6 (6 – 6) days, resulting in a total of 6074 valid PA days, of which 4049 (67%) were weekdays. Table 2 presents the daily PA measures during the weekdays. The smallest amount of time and lowest energy expenditure (EE) were spent in moderate-to-vigorous intensity. At this intensity, patients spent a median of 6 (0 – 22) min·day-1 in bouts of ≥10 minutes and 38 (17 – 79) min·day-1 in bouts of ≥2 minutes. Figure 1 presents the daily PA hourly patterns of the patients. A similar pattern can be observed between weekdays (Figure 1A) and weekend days (Figure 1B), and in both analyses the peak of intensity occurred before midday.

**Table 2** Daily physical activity measures during weekdays in patients with COPD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **General physical activity** | | | |
| **PA measure** | Very light intensity | Light intensity | | Moderate-to-vigorous intensity |
| Time, min∙day-1  Before midday  After midday  Total | 283 (236 – 347)  514 (449 – 577)  803 (710 – 901) | 49 (31 – 74)†  88 (53 – 123)†  142 (92 – 194)† | | 21 (10 – 42)†,‡  27 (13 – 59)†,‡  52 (26 – 99)†,‡ |
| EE, METs-min∙day-1  Before midday  After midday  Total | 364 (274 – 502)  668 (521 – 858)  1032 (822 – 1327) | 154 (95 - 263)†  273 (167 – 413)†  435 (291 – 655)† | | 110 (46 – 232)†,‡  147 (65 – 310)†,‡  267 (132 – 550)†,‡ |
|  | Bouts of physical activity | | | |
| PA measure | Very light intensity | | Light intensity | Moderate-to-vigorous intensity |
| Time, min∙day-1\*  ≥2-minute  Before midday  After midday  Total  ≥10-minute  Before midday  After midday  Total | 273 (225 – 338)  503 (435 – 569)  781 (683 – 884)  215 (167 – 284)  436 (352 – 526)  657 (539 – 780) | | 37 (22 – 59)†  67 (37 – 97)†  107 (65 – 156)†  3 (0 – 8)†  4 (0 – 14)†  7 (0 – 22)† | 15 (6 – 34)†,‡  20 (8 – 47)†,‡  38 (17 – 79)†,‡  2 (0 – 11)†  3 (0 – 13)†,‡  6 (0 – 22)† |
| Frequency, bouts∙day-1\*  ≥2-minute  Before midday  After midday  Total  ≥10-minute  Before midday  After midday  Total | 21 (17 – 25)  27 (21 – 34)  48 (39 – 58)  7 (6 – 9)  11 (9 – 13)  18 (16 – 21) | | 11 (7 – 16)†  19 (11 – 26)†  31 (20 – 41)†  0 (0 – 1)†  0 (0 – 1)†  1 (0 – 2)† | 4 (2 – 8)†,‡  5 (2 – 10)†,‡  10 (5 – 17)†,‡  0 (0 – 1)†  0 (0 – 1)†  1 (0 – 2)† |
| Average duration, min∙bout-1\*  ≥2-minute  Before midday  After midday  Total  ≥10-minute  Before midday  After midday  Total | 13 (10 – 17)  18 (13 – 27)  16 (12 – 21)  29 (24 – 36)  37 (29 – 50)  34 (28 – 43) | | 3 (3 – 4)†  3 (3 – 4)†  3 (3 – 4)†  10 (0 – 13)†  11 (0 – 13)†  12 (0 – 14)† | 4 (3 – 5)†,‡  4 (3 – 5)†,‡  4 (3 – 5)†,‡  10 (0 – 15)†,‡  11 (0 – 15)†  13 (0 – 16)†,‡ |
| EE, METs-min∙day-1\*  ≥2-minute  Before midday  After midday  Total  ≥10-minute  Before midday  After midday  Total | 347 (261 – 490)  648 (501 – 845)  1000 (783 – 1298)  273 (193 – 411)  572 (410 – 783)  847 (626 – 1168) | | 118 (67 – 205)†  211 (119 – 335)†  340 (204 – 523)†  6 (0 – 26)†  14 (0 – 47)†  26 (0 – 77)† | 86 (29 – 187)†,‡  106 (41 – 255)†,‡  205 (86 – 436)†,‡  9 (0 – 61)†,‡  12 (0 – 69)†  36 (0 – 132)† |

Data expressed as median (interquartile range). EE: energy expenditure; MET: metabolic equivalent of task. \*The time, frequency and EE in bouts of physical activity were averaged out over the total number of valid days, whilst the duration of bouts of physical activity was averaged out over the total number of bouts available. †*P*<0.05 vs very light intensity; ‡*P*<0.05 vs light intensity.

***Stratification for clinical characteristics***

Patients of older age, female gender, LTOT users, lower DLCO, higher mMRC dyspnea grade, higher BMI, higher ADO index, higher GOLD grade and patients from GOLD group D spent the smallest amount of time and lowest EE in moderate-to-vigorous intensity (Tables E3-E11, online supplement). Daily PA hourly patterns after stratification for the abovementioned clinical characteristics are presented in figures 2 and E1 (online supplement), showing a noticeable influence of age, BMI, mMRC dyspnea grades, and ADO index scores. The influence of GOLD grades or groups on these patterns was small. A weak but significant positive association existed between FEV1 (% predicted) and the time in activities of moderate-to-vigorous intensity (*r*s=0.20, *P*<0.0001; Figure 3).

***Patients with COPD versus healthy subjects***

Table 3 presents the general characteristics and daily PA measures in moderate-to-vigorous intensity of 66 healthy subjects and a subgroup of 66 patients with COPD, pairwise-matched for gender, age and BMI. As expected, subjects with COPD had worse lung function, higher mMRC dyspnea grade and worse PA measures compared to healthy subjects. The comparison of daily PA measures in very light and light intensities can be found in Table E12 (online supplement). Interestingly, patients with COPD spent more time in very light intensity than healthy subjects, but there was no difference for the time in light intensity. Figure 4 presents the daily PA hourly patterns of both groups. In general, healthy subjects performed their activities at higher intensities compared to patients with COPD, and this difference was more pronounced during weekdays.

**Table 3** General characteristics and daily physical activity measures in moderate-to-vigorous intensity of healthy subjects and matched patients with COPD

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic/PA measure** | **Healthy subjects** | **Matched patients with COPD** | ***P*-value** |
| General characteristics  N | 66 | 66 |  |
| Age, yrs | 65 (61 – 70) | 65 (61 – 70) | 1.00 |
| Male, % | 45 | 45 | 1.00 |
| BMI, kg·m-2 | 25.3 (22.9 – 28.1) | 24.9 (22.4 – 27.9) | 0.65 |
| FEV1, % predicted | 107 (97 – 117) | 43 (29 – 63) | <0.0001 |
| FEV1/FVC, % | 78 (75 – 82) | 42 (32 – 54) | <0.0001 |
| mMRC dyspnea grade, points\* | 0 (0 – 0) | 2 (1 – 3) | <0.0001 |
| Physical activity measures in moderate-to-vigorous intensity  Time, min∙day-1 | 101 (57 – 163) | 47 (30 – 95) | <0.0001 |
| EE, METs-min∙day-1 | 461 (271 – 797) | 213 (123 – 435) | <0.0001 |
| Time in ≥2-min bouts, min∙day-1 | 82 (38 – 138) | 37 (15 – 83) | <0.0001 |
| Time in ≥10-min bouts, min∙day-1 | 29 (10 – 73) | 6 (0 – 20) | <0.0001 |
| Frequency of ≥2-min bouts, bouts∙day-1 | 17 (10 – 25) | 9 (5 – 17) | <0.0001 |
| Frequency of ≥10-min bouts, bouts∙day-1 | 2 (1 – 4) | 0 (0 – 1) | <0.0001 |
| Average duration of ≥2-min bouts, min∙bout-1 | 5 (4 – 7) | 4 (3 – 5) | <0.0001 |
| Average duration of ≥10-min bouts, min∙bout-1 | 16 (13 – 21) | 12 (0 – 14) | <0.0001 |
| EE in ≥2-min bouts, METs-min∙day-1 | 362 (212 – 712) | 164 (65 – 376) | <0.0001 |
| EE in ≥10-min bouts, METs-min∙day-1 | 107 (47 – 417) | 23 (0 – 121) | <0.0001 |

Data expressed as absolute/relative frequency, or median (interquartile range). See Tables 1 and 2 for definition of abbreviations. \*Data available for 48 healthy subjects and 59 patients with COPD.

**Cluster analysis of daily PA measures**

The PCA identified 3 components, which accounted for 60% of the total variance (first component, 34%; second component, 17%; third component, 9%). The most relevant features in each component are described in the online supplement. Cluster analysis, performed on the 3 PCA components, identified five groups (Figure 5; see online supplement for a 3D video of Figure 5). Table 4 presents the general characteristics and PA measures of these groups. Cluster 1 was characterized by higher BMI, more dyspnea, higher ADO index, more time and EE in very light intensity, and less time and EE in light and moderate-to-vigorous intensities compared to other clusters. This cluster also had worse lung function compared to clusters 3 and 4, and apparently a higher proportion of GOLD D patients. Cluster 2 had the largest sample size with the most similar general characteristics and PA measures to the total sample. Cluster 2 also had more dyspnea and a higher ADO index than clusters 3 and 5. Similarly to cluster 1, this cluster spent more time and EE in very light intensity, and less time and EE in moderate-to-vigorous intensity than other clusters. Cluster 3 exhibited a higher FEV1 than cluster 2 and a higher FEV1/FVC ratio than clusters 1 and 2, whilst cluster 4 was younger than clusters 1 and 2 and had a lower BMI compared to cluster 2. Moreover, cluster 3 spent more time and EE in light intensity and less time and EE in moderate-to-vigorous intensity than clusters 4 and 5, whilst cluster 4 spent more time in light intensity compared to cluster 5. Cluster 5 had the smallest sample size (n=21) and was characterized by less time in very light intensity and more time in moderate-to-vigorous intensity compared to other clusters. Figure 6 presents the daily PA hourly patterns of the clusters. In all clusters the peak of intensity during the day occurred before midday, and in general, weekdays and weekend days presented a similar pattern, especially in more inactive clusters.

**Table 4** General characteristics and daily physical activity measures of clusters of patients with COPD

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic/PA measure** | **Cluster 1**  **(very long very light intensity/very short moderate-to-vigorous intensity)** | **Cluster 2**  **(very long very light intensity/ short moderate-to-vigorous intensity)** | **Cluster 3**  **(long very light intensity/short moderate-to-vigorous intensity)** | **Cluster 4**  **(long very light intensity/long moderate-to-vigorous intensity)** | **Cluster 5**  **(intermediate very light intensity/very long moderate-to-vigorous intensity)** | ***P*-value** |
| General characteristics  N | 216 | 415 | 184 | 165 | 21 |  |
| Age, yrs | 68 (62 – 74) | 67 (61 – 72) | 67 (60 – 72) | 63 (58 – 70)†,‡ | 63 (56 – 68) | <0.0001 |
| Male, % | 67 | 67 | 51 | 76 | 67 | 0.32 |
| BMI, kg·m-2 | 30.4 (26.5 – 34.7) | 25.7 (22.6 – 29.0)† | 24.9 (22.2 – 27.4)† | 23.1 (20.3 – 26.8)†,‡ | 22.5 (18.3 – 30.9)† | <0.0001 |
| FEV1, % predicted | 44 (32 – 58) | 48 (34 – 61) | 57 (41 – 71)†,‡ | 50 (36 – 68)† | 51 (39 – 70) | <0.0001 |
| FEV1/FVC, % | 43 (34 – 55) | 44 (34 – 55) | 50 (38 – 61)†,‡ | 47 (36 – 57) | 49 (38 – 64) | 0.002 |
| mMRC dyspnea grade, points\* | 2 (1 – 3) | 2 (1 – 3)† | 1 (1 – 2)†,‡ | 1 (0 – 3)† | 1 (0 – 2)†,‡ | <0.0001 |
| ADO index\* | 5 (3 – 6) | 4 (3 – 5)† | 4 (3 – 5)†,‡ | 4 (3 – 5)† | 3 (2 – 4)†,‡ | <0.0001 |
| GOLD 2007 classification 1 / 2 / 3 / 4, % | 4 / 34 / 43 / 19 | 8 / 38 / 35 / 19 | 18 / 46 / 23 / 13 | 9 / 42 / 31 / 18 | 10 / 43 / 33 / 14 | 0.17 |
| GOLD 2011 classification A / B / C / D, %\* | 18 / 19 / 16 / 47 | 28 / 15 / 17 / 40 | 44 / 16 / 16 / 24 | 31 / 13 / 20 / 36 | 44 / 6 / 28 / 22 | 0.02 |
| Physical activity measures in very light intensity  Time, min∙day-1 | 955 (904 – 1042) | 823 (768 – 879)† | 706 (641 – 769)†,‡ | 675 (604 – 735)†,‡ | 516 (456 – 621)†,‡,§ | <0.0001 |
| EE, METs-min∙day-1 | 1356 (1165 – 1730) | 1022 (854 - 1222)† | 855 (729 – 1118)†,‡ | 789 (692 – 1019)†,‡ | 853 (661 – 1884)† | <0.0001 |
| Time in ≥2-min bouts, min∙day-1 | 946 (894 – 1033) | 802 (746 – 858)† | 682 (611 – 744)†,‡ | 647 (573 – 707)†,‡ | 480 (428 – 591)†,‡,§ | <0.0001 |
| Time in ≥10-min bouts, min∙day-1 | 890 (815 – 968) | 680 (622 – 745)† | 534 (452 – 601)†,‡ | 490 (415 – 561)†,‡ | 340 (254 – 444)†,‡,§ | <0.0001 |
| Frequency of ≥2-min bouts, bouts∙day-1 | 33 (26 – 39) | 50 (42 – 57)† | 54 (48 – 61)†,‡ | 54 (47 – 65)†,‡ | 46 (43 – 59)† | <0.0001 |
| Frequency of ≥10-min bouts, bouts∙day-1 | 17 (14 – 20) | 20 (17 – 22)† | 18 (16 – 20)†,‡ | 17 (15 – 20)‡ | 12 (11 – 16)†,‡,§,ǁ | <0.0001 |
| Average duration of ≥2-min bouts, min∙bout-1 | 29 (23 – 36) | 16 (14 – 19)† | 12 (10 – 15)†,‡ | 11 (10 – 14)†,‡ | 10 (8 – 13)†,‡ | <0.0001 |
| Average duration of ≥10-min bouts, min∙bout-1 | 53 (43 – 65) | 35 (30 – 41)† | 29 (25 – 34)†,‡ | 27 (24 – 32)†,‡ | 26 (22 – 32)†,‡ | <0.0001 |
| EE in ≥2-min bouts, METs-min∙day-1 | 1344 (1145 – 1709) | 988 (827 – 1186)† | 810 (687 – 1074)†,‡ | 748 (650 – 976)†,‡ | 832 (606 – 1730)† | <0.0001 |
| EE in ≥10-min bouts, METs-min∙day-1 | 1257 (1068 – 1632) | 836 (693 – 1050)† | 628 (516 – 862)†,‡ | 589 (467 – 779)†,‡ | 704 (420 – 1185)† | <0.0001 |
| Physical activity measures in light intensity  Time, min∙day-1 | 57 (35 – 79) | 139 (113 – 167)† | 245 (208 – 282)†,‡ | 167 (134 – 209)†,‡,§ | 121 (87 – 163)†,§,ǁ | <0.0001 |
| EE, METs-min∙day-1 | 196 (121 – 305) | 408 (320 – 517)† | 725 (591 – 958)†,‡ | 526 (366 – 735)†,‡,§ | 416 (227 – 1093)†,§ | <0.0001 |
| Time in ≥2-min bouts, min∙day-1 | 38 (19 – 56) | 105 (85 – 130)† | 205 (175 – 244)†,‡ | 126 (97 – 161)†,‡,§ | 79 (50 – 120)†,§,ǁ | <0.0001 |
| Time in ≥10-min bouts, min∙day-1 | 0 (0 – 3) | 8 (3 – 16)† | 46 (32 – 65)†,‡ | 8 (3 – 16)†,§ | 0 (0 – 4)‡,§,ǁ | <0.0001 |
| Frequency of ≥2-min bouts, bouts∙day-1 | 13 (7 – 17) | 30 (24 – 36)† | 49 (40 – 56)†,‡ | 37 (31 – 46)†,‡,§ | 28 (20 – 37)†,§,ǁ | <0.0001 |
| Frequency of ≥10-min bouts, bouts∙day-1 | 0 (0 – 0) | 1 (0 – 1)† | 3 (2 – 5)†,‡ | 1 (0 – 1)†,§ | 0 (0 – 0)‡,§ | <0.0001 |
| Average duration of ≥2-min bouts, min∙bout-1 | 3 (3 – 3) | 3 (3 – 4)† | 4 (4 – 5)†,‡ | 3 (3 – 4)†,§ | 3 (3 – 3)‡,§,ǁ | <0.0001 |
| Average duration of ≥10-min bouts, min∙bout-1 | 0 (0 – 11) | 12 (11 – 13)† | 14 (13 – 15)†,‡ | 12 (10 – 14)†,§ | 0 (0 – 11)‡,§,ǁ | <0.0001 |
| EE in ≥2-min bouts, METs-min∙day-1 | 131 (68 – 215) | 317 (241 – 408)† | 620 (510 – 801)†,‡ | 390 (263 – 586)†,‡,§ | 307 (159 – 748)†,§ | <0.0001 |
| EE in ≥10-min bouts, METs-min∙day-1 | 0 (0 – 12) | 26 (10 – 54)† | 155 (99 – 240)†,‡ | 26 (8 – 54)†,§ | 0 (0 – 19)‡,§,ǁ | <0.0001 |
| Physical activity measures in moderate-to-vigorous intensity  Time, min∙day-1 | 15 (7 – 27) | 48 (30 – 70)† | 68 (43 – 96)†,‡ | 166 (136 – 219)†,‡,§ | 361 (332 – 458)†,‡,§ | <0.0001 |
| EE, METs-min∙day-1 | 90 (40 – 192) | 235 (138 – 349)† | 327 (198 – 527)†,‡ | 805 (616 – 1134)†,‡,§ | 2693 (1694 – 5886)†,‡,§ | <0.0001 |
| Time in ≥2-min bouts, min∙day-1 | 9 (4 – 19) | 36 (20 – 54)† | 51 (29 – 72)†,‡ | 145 (118 – 190)†,‡,§ | 336 (293 – 433)†,‡,§ | <0.0001 |
| Time in ≥10-min bouts, min∙day-1 | 0 (0 – 3) | 5 (0 – 14)† | 9 (3 – 18)†,‡ | 60 (38 – 91)†,‡,§ | 209 (161 – 317)†,‡,§ | <0.0001 |
| Frequency of ≥2-min bouts, bouts∙day-1 | 3 (1 – 5) | 9 (6 – 13)† | 13 (8 – 17)†,‡ | 26 (20 – 33)†,‡,§ | 41 (35 – 52)†,‡,§ | <0.0001 |
| Frequency of ≥10-min bouts, bouts∙day-1 | 0 (0 – 0) | 0 (0 – 1)† | 1 (0 – 1)†,‡ | 3 (2 – 5)†,‡,§ | 10 (8 – 13)†,‡,§ | <0.0001 |
| Average duration of ≥2-min bouts, min∙bout-1 | 3 (2 – 4) | 4 (3 – 5)† | 4 (3 – 5)† | 6 (5 – 7)†,‡,§ | 8 (7 – 11)†,‡,§ | <0.0001 |
| Average duration of ≥10-min bouts, min∙bout-1 | 0 (0 – 11) | 12 (0 – 14)† | 13 (10 – 16)†,‡ | 17 (15 – 21)†,‡,§ | 20 (17 – 25)†,‡,§ | <0.0001 |
| EE in ≥2-min bouts, METs-min∙day-1 | 56 (20 – 123) | 173 (92 – 280)† | 251 (146 – 392)†,‡ | 704 (544 – 992)†,‡,§ | 2583 (1589 – 5348)†,‡,§ | <0.0001 |
| EE in ≥10-min bouts, METs-min∙day-1 | 0 (0 – 20) | 25 (0 – 70)† | 47 (13 – 105)†,‡ | 300 (171 – 513)†,‡,§ | 1635 (1102 – 2590)†,‡,§ | <0.0001 |

Data expressed as absolute/relative frequency, or median (interquartile range). See Tables 1 and 2 for definition of abbreviations. \*Data available for 198 subjects in Cluster 1, 367 subjects in Cluster 2, 159 subjects in Cluster 3, 126 subjects in Cluster 4, and 18 subjects in Cluster 5; †*P*<0.05 vs Cluster 1; ‡*P*<0.05 vs Cluster 2; §*P*<0.05 vs Cluster 3; ǁ*P*<0.05 vs Cluster.

**DISCUSSION**

The present study provides detailed analyses of objectively measured PA in a multinational sample of 1001 patients with COPD. The principal findings were that, in patients with COPD, daily PA measures and hourly patterns vary considerably after stratification for clinical characteristics. Also, patients with COPD exhibit PA hourly patterns at lower intensities in comparison with healthy subjects. Furthermore, patients with COPD can be clustered based on daily PA measures, with 5 clusters being identified, each with distinct PA measures and hourly patterns.

**Daily PA measures and PA hourly patterns in COPD**

Our results clearly show that PA is a heterogeneous outcome in patients with COPD, corroborating previous findings (1, 34, 35)(ADDrefGimeno-Santos2014). Distinct daily PA measures were found after stratification for most clinical characteristics investigated in our study (Table E3-E11). Interestingly, comparable time in very light and moderate-to-vigorous intensities was found between GOLD groups A and C, and B and D (Table E11). This suggests that symptoms, which discriminated between groups A/C and B/D, are better associated with PA measures than the degree of airflow limitation, which discriminated between groups A/B and C/D. Nonetheless, the influence of the GOLD 2011 classification on PA hourly patterns was less evident. In fact, only age, BMI, mMRC dyspnea grade, and ADO index scores seemed to associate with PA hourly patterns (Figures 2 and E1).

Patients with COPD are physically less active compared to healthy subjects (1, 3, 32, 37). The present study is the first to confirm this finding after a pairwise matching for gender, age and BMI. Moreover, patients with COPD performed their activities at a lower intensity compared with healthy subjects (Figure 4), and this difference was more evident during weekdays. To our knowledge, this study is the first large study to show that patients with COPD not only spend less time in moderate-to-vigorous intensity, but also more time in very light intensity, which can be considered a surrogate of sedentary time (i.e., activities between 1.0-1.5 METs) (38). Reducing the time in very light intensity without necessarily increasing the time in moderate-to-vigorous intensity may be an important strategy for achieving health benefits in patients with COPD ([4](#_ENREF_4)).

**Clusters of patients with COPD based on daily PA measures**

The present study is the first to cluster patients with COPD based on daily PA measures. Indeed, five clusters were identified, each with distinct PA measures and hourly patterns. One very active cluster and one very inactive cluster were identified, but clusters in intermediate categories were also observed. Of note, cluster 1 spent less time in moderate-to-vigorous intensity and more time in very light intensity compared to other clusters, with a very similar PA hourly pattern between weekdays and weekend days. This cluster is representative of an inactive lifestyle.

Only a few studies have used objectively measured PA data solely for clustering subjects. In 10-to-12-year-old children, De Bourdeaudhuij and colleagues (40) were able to identify a cluster with a mixed arrangement of PA (i.e., less time in moderate-to-vigorous intensity + less sedentary time). In our study, we also found a cluster with resembling characteristics (i.e., cluster 4, long very light intensity/long moderate-to-vigorous intensity), confirming that activities of moderate-to-vigorous intensity and sedentary activities are not two sides of one continuum (40). On the other hand, more inactive clusters were also observed (clusters 1, 2 and 3). In middle-aged Chinese adults, Lee et al ([18](#_ENREF_18)) observed that male subjects from the least active cluster presented higher body fat percentage and older age than those from the active group ([18](#_ENREF_18)). In our study, patients from cluster 1 had older age, lower FEV1, higher BMI, worse dyspnea and higher ADO index than other clusters. Based on their characteristics, patients from this cluster may have a worse prognosis, but no follow-up data is available to confirm this hypothesis.

**Strengths, relevance and limitations of the findings**

Our sample is by far the largest and most diverse sample of patients with COPD with objectively assessed PA data ever studied. This allowed detailed analyses of daily PA, even identifying clusters of patients with COPD with similar PA measures, a true novelty within the COPD literature. PA hourly patterns were also investigated for the first time in a large-scale study in COPD, another important advance. All these analyses were only possible due to the use of objective methods of PA, another strength of our study.

Our findings are of importance for future research and clinical practice. Most clinical characteristics investigated in our study associated importantly with PA measures, but not all with PA hourly patterns. This suggests that subjects with certain clinical characteristics might have different amounts of daily PA, but still have a similar pattern of PA during their day. We also observed that, compared with matched healthy subjects, patients with COPD are not only less active but also more sedentary. Future studies aiming behavior changes in terms of PA in COPD should focus on both activities of moderate-to-vigorous intensity and sedentary activities. Finally, we were able to identify groups of patients with specific PA profiles, which can be useful to tailor interventions according to the needs of each group. This may lead to more important improvements in PA, which is particularly interesting as interventions thus far have failed to increase importantly PA measures in patients with COPD ([13](#_ENREF_13" \o "Deering, 2011 #382), [16](#_ENREF_16" \o "Cindy Ng, 2012 #236), [17](#_ENREF_17" \o "Steele, 2008 #249)).

Some methodological limitations are acknowledged. Selection and information biases might be present, as parts of the data were collected with different purposes. Nevertheless, having patients from different studies and countries allowed us to have a more diverse sample, which may enhance the external validity of our findings. The clusters identified in our study were not validated, and this constitutes another limitation. Moreover, other important outcomes that could help to characterise the clusters, such as comorbidities, were not investigated. Some of our findings need to be interpreted with caution in light of the number of multiple comparison tests performed.(41) Nonetheless, multiple findings in the same direction rather than a single statistically significant result are suggestive that these are not due to chance alone.

In a large and multicenter sample of patients with COPD, daily PA measures and hourly patterns were found to vary considerably depending on the clinical characteristic. Compared with healthy subjects, patients spent not only less time in higher intensities of physical activity, but also more time in lower intensities. Five clusters of patients were identified, each with distinct PA measures and hourly patterns. The present data show that outcome measures need to be clearly delineated when evaluating interventions aiming to promote PA in patients with COPD.

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**Data sharing statement** Data sharing is not available.

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**FIGURE LEGENDS**

**Figure 1** Daily physical activity hourly patterns of the 1001 patients with chronic obstructive pulmonary disease during weekdays (A) and weekend days (B). Data pooled per hour as mean (95% confidence intervals).

**Figure 2** Daily physical activity hourly patterns of the patients with chronic obstructive pulmonary disease after stratification for: A and B – modified Medical Research Council (mMRC) grades, data available for 868 subjects only; C and D – body mass index (BMI) classification; E and F – Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades (1 to 4); and G and H – GOLD groups (A to D). Figures A, C, E, and G represent weekdays, whilst figures B, D, F, and H represent weekend days. Data pooled per hour as mean (95% confidence intervals).

**Figure 3** Spearman’s correlation between forced expiratory volume in the first second (% predicted) and the daily time in activities of moderate-to-vigorous intensity for 1001 patients with chronic obstructive pulmonary disease (*r*s=0.20, *P*<0.0001).

**Figure 4** Daily physical activity hourly patterns of healthy subjects and matched patients with chronic obstructive pulmonary disease during weekdays (A) and weekend days (B). Data pooled per hour as mean (95% confidence intervals).

**Figure 5** The five clusters identified. A: Graph in 3 dimensions presenting the three principal component analysis (PCA) components; B: Graph in 2 dimensions presenting the 1st and 2nd components; C: Graph in 2 dimensions presenting the 1st and 3rd components; and D: Graph in 2 dimensions presenting the 2nd and 3rd components. Details about the relationship between components and clusters can be found in the online supplement.

**Figure 6** Daily physical activity hourly pattern of the clusters of patients with chronic obstructive pulmonary disease during weekdays (A and C) and weekend days (B and D), and before (A and B) and after (C and D) synchronization of the waking up moment. Data pooled per hour as mean (95% confidence intervals).