**Physical activity patterns and clusters in 1001 patients with COPD**

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**Abstract**

**Background**

Physical activity levels in chronic obstructive pulmonary disease (COPD) have been mostly presented as an average of multiple measurement days. However, physical activity is a multi-dimensional construct meaning that it has much more relevant descriptors and components beside its total amount.

We described physical activity measures and hourly patterns in patients with COPD after stratification for generic and COPD-specific characteristics and, based on multiple physical activity measures, we identified clusters of patients.

**Methods**

1001 patients with COPD (65% men; age, 67 years; FEV1, 49% predicted) were studied cross-sectionally. Daily physical activity measures and hourly patterns (i.e., a graphic representation of the mean intensity of activity per hour during the course of a day) were analysed based on data from a multi-sensor armband. Principal component analysis (PCA) and cluster analysis were applied to physical activity measures to identify clusters of patients with COPD.

**Results**

Age, body mass index (BMI), dyspnoea grade, ADO index (including age, dyspnoea, and airflow obstruction), sex, long-term oxygen therapy use, lung diffusion capacity, and GOLD classification were associated with physical activity measures in patients with COPD (*P*<0.05 for all), but only the first four characteristics/parameters were associated with hourly patterns. Five clusters were identified based on three PCA components, which accounted for 60% of variance. Importantly, cluster 1 (i.e., the most inactive patients) was characterized by higher BMI, lower FEV1, worse dyspnoea and higher ADO index compared to other clusters (*P*<0.05 for all).

**Conclusions**

Daily physical activity measures and hourly patterns are heterogeneous in COPD. Clusters of patients were identified solely based on physical activity data. These findings may be useful to develop interventions aiming to promote physical activity in COPD.

**Introduction**

Physical activity levels in patients with chronic obstructive pulmonary disease (COPD) are mostly presented as a total amount or as an average of multiple measurement days [1-6]. Nevertheless, physical activity is a multi-dimensional construct which should be described by appropriate descriptors and components [7]. A more detailed approach to physical activity data analysis could provide complementary information about the physical activity behavior of patients with COPD. For example, patients with COPD have shown to perform bouts of moderate-to-vigorous physical activity, but the proportion of time in bouts over total time in physical activity and the frequency of bouts decreased with increasing disease severity [8].

Studies in different patient populations show that a more detailed analysis of physical activity can be achieved by plotting physical activity hourly patterns [7, 9, 10] and by applying cluster analysis to physical activity measures [9, 11, 12]. Physical activity hourly patterns provide a graphic representation of the temporal trends of physical activity intensities over the course of a day [7, 9, 10] and they have been shown to provide discriminating patients' information.

Rochester et al [13], for example, observed a delayed morning start and a reduced peak of activity in patients with Parkinson’s disease, while, Evering and coworkers [14] observed a less physically active pattern in the afternoon and evening in patients with chronic fatigue syndrome when compared with controls. Cluster analysis, in turn, could be useful to identify subgroups of subjects with distinct physical activity characteristics. In middle-aged Chinese adults, Lee et al [9] were able to identify two clusters of subjects, one more active than the other. Male subjects in the least active cluster had higher body fat percentage and older age than those in the active group. These detailed analyses could thenlead to new insights regarding subgroups of patients with COPD with specific physical activity patterns, which may be used in further investigations and tailored intervention strategies [6, 16, 17]. Indeed, for specific groups of patients greater and/or more sustainable results may be achieved if the focus shifts from an increase in moderate-to-vigorous activities towards a reduction in sedentary time [18-20].

Therefore, the main contributions provided by this work are: to describe physical activity measures and physical activity hourly patterns in patients with COPD after stratification for generic and COPD-specific characteristics; and to identify clusters of patients with COPD based on physical activity measures.

**Materials and Methods**

*Please, see File S1 for all details.*

**Study Design and Participants**

In this retrospective, multicentre, cross-sectional study, objectively assessed physical activity data from 10 countries (i.e., United Kingdom, Ireland, the Netherlands, Germany, Switzerland, Italy, Spain, the United States of America, Brazil, and Australia) were analysed. Published and/or unpublished physical activity data from previous studies as assessed by the SenseWear Armband or SenseWear Mini Armband activity monitors (both from BodyMedia Inc., Pittsburgh, PA, USA) were considered for analysis. From all studies, only the baseline data were used (in studies that included longitudinal analyses), which means that the participants were not undergoing any specific intervention by the time of assessment. Subjects were included if they had COPD with a post-bronchodilator forced expiratory volume in the first 1 second (FEV1) / forced vital capacity (FVC) ratio <0.70 [21], they were clinically stable at the time of physical activity assessment, and they had complete data for age, sex, body mass index (BMI) and daily physical activity measures. Ethics Board approval was obtained from the local ethics committees/institutional review boards (details of the ethics committees/institutional review boards can be found in File S1), and written informed consent was provided by participants, except for the data from Italy (n=23) which were obtained as part of routine clinical assessments. The Italian data, however, were de-identified to protect patient information confidentiality.

**Assessments**

Demographics, anthropometrics, lung function, and clinical data were assessed. In order to investigate their association with physical activity measures and hourly patterns, these outcomes were stratified according to established criteria or according to the median value (i.e., above or below the median). Both the SenseWear Armband or SenseWear Mini Armband activity monitors use multisensory data in combination with pattern recognition algorithms to reliably estimate energy expenditure (EE) and metabolic equivalent of task (MET) [REF]that were used in turn to assess physical activity [22-25]. METs data are divided into activity intensity levels using the thresholds proposed by the American College of Sports Medicine [26]: very light intensity, <2.0 metabolic equivalents of task (METs); light intensity, 2.0 to 2.9 METs; and moderate-to-vigorous intensity, ≥3.0 METs.

Subjects with a minimum of four recorded days (two weekdays + Saturday + Sunday) [1] with the device being used for ≥22 hours·day-1 [27] were included in the analyses. Only recordings during waking hours of weekdays were considered for the cluster analysis, since physical activity measures during the weekend are known to be different [1] and therefore could bias the analyses. The physical activity measures represent the average of all valid weekdays. Weekend days were used only for the presentation of daily physical activity hourly patterns. All values are represented by absolute values. Values relative to peak exercise capacity were not presented as measurement of maximal exercise capacity was not available. For the clustering of patients, a set of relevant variables were generated after stratifying averages of physical activity measures according to different criteria (i.e., intensity, duration, period of the day, frequency and quantity, or the combination of these criteria; S1 Table in File S1). Data regarding the steps-per-day were not included in the current analysis as this outcome is subject to inaccuracy unless the subject walks at higher speeds [28].

**Statistical Analyses**

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; significant if *P*<0.05) was used for comparing continuous variables, while the chi-square test was used for categorical variables. The influence of seasons on daily physical activity measures was minimal (S2 Table in File S1) and therefore it was not taken into consideration throughout the analyses. Spearman coefficient was used to investigate correlations, when appropriate. The area under each hourly pattern, named as the Area Under the Curve (AUC), was calculated and presented with its 95% confidence intervals in order to quantitatively represent time-varying averages of the hourly patterns. *P*<0.01 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).

Cluster analysis was adopted to identify subgroups with distinct physical activity profiles. Firstly, Principal Component Analysis (PCA) was used to compress the information contained in the high-dimensional feature set (180 dimensions) to a lower subspace (three dimensions) that is both convenient for data visualization and able to account for the desired variance of the data (set to 60%). The features were initially standardized using z-scores. Secondly, a k-means clustering algorithm with automatic selection of the number of clusters was applied to the three principal components 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 [29]. The normalized mean over pairwise clustering distances was used as instability measure [29]. Feature extraction, PCA and cluster analysis were performed using Matlab R2012b (Mathworks Inc., USA).

**Results**

**General Characteristics**

In total, 1001 patients with COPD were analysed (Table 1). The majority of patients were men, had a normal-to-overweight BMI, moderate-to-severe degree of airflow limitation, and only a small proportion used long-term oxygen therapy (LTOT). Compared to female subjects, male subjects were slightly older (67 (62 – 73) versus 65 (59 – 71) years; *P*<0.0001) and had higher BMI (26.5 (23.3 – 29.9) versus 24.5 (21.1 – 28.6) kg·m-2; *P*<0.0001), but no differences were found in FEV1, modified Medical Research Council (mMRC) grades, or Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 and 2011 classifications (*P*>0.01 for all). Characteristics per country can be found in S3 Table in File S2.

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

|  |  |  |
| --- | --- | --- |
| **Characteristic** |  | **Value** |
| Age, years |  | 67 (61 – 72) |
| Male, % |  | 65 |
| BMI, kg·m-2 |  | 25.8 (22.5 – 29.6) |
| BMI classification, % |  |  |
|  | Underweight | 7 |
|  | Normal weight | 37 |
|  | Overweight | 34 |
|  | Obese | 22 |
| mMRC dyspnoea 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, points\* |  | 4 (3 – 5) |
| GOLD 2007 classification, % |  |  |
|  | 1 | 9 |
|  | 2 | 40 |
|  | 3 | 34 |
|  | 4 | 17 |
| GOLD 2011 classification, %\* |  |  |
|  | A | 29 |
|  | B | 16 |
|  | C | 17 |
|  | D | 38 |

Data expressed as 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, dyspnoea, and airflow 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 Physical Activity Measures and Physical Activity Hourly Patterns**

The median number of valid days was 6 (6 – 6) days, resulting in a total of 6074 valid physical activity days, of which 4049 (67%) were weekdays. Table 2 presents the daily physical activity measures during the weekdays. The smallest value of the daily total time and lowest values of the daily total energy expenditure (EE) were reported for moderate-to-vigorous intensity activity level. At this intensity, patients spent a median of 6 (0 – 22) min·day-1 in bouts of ≥10 minutes. This value is lower than 10 minutes due to the averaging process, in which days without bouts of ≥10 minutes were also taken into account. Daily hourly patterns were similar between weekdays and weekend days, with the peak of intensity occurring before midday (Fig. 1). This similarity was confirmed by the AUC-values (0.30 for weekdays and 0.29 for weekend days; S4 Table in File S2).

**Fig. 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).

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Physical activity measure** | **Very light intensity** | **Light intensity** | **Moderate-to-vigorous intensity** |
| **General physical activity** |  |  |  |
| Time, min∙day-1 | 803 (710 – 901) | 142 (92 – 194)† | 52 (26 – 99)†,‡ |
| EE, METs-min∙day-1 | 1032 (822 – 1327) | 435 (291 – 655)† | 267 (132 – 550)†,‡ |
| **≥10-minute bouts of physical activity** |  |  |  |
| Time, min∙day-1\* | 657 (539 – 780) | 7 (0 – 22)† | 6 (0 – 22)† |
| Frequency, bouts∙day-1\* | 18 (16 – 21) | 1 (0 – 2)† | 1 (0 – 2)† |
| Average duration, min∙bout-1\* | 32 (27 – 39) | 13 (12 – 14)† | 14 (12 – 17)†,‡ |
| EE, METs-min∙day-1\* | 847 (626 – 1168) | 26 (0 – 77)† | 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, while 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 Generic and COPD-specific Characteristics**

In general, patients of older age, female sex, LTOT users, lower diffusion capacity of the lung for carbon monoxide (DLCO), higher mMRC dyspnoea grade, higher BMI, higher ADO index (including age, dyspnoea, and airflow obstruction), higher GOLD grade and patients from GOLD group D spent the smallest daily total time and lowest daily total EE in moderate-to-vigorous intensity (S5-S13 Tables in File S2). Daily physical activity hourly patterns after stratification for the abovementioned characteristics are presented in fig. 2 and fig. S1, showing a significant influence of age, BMI, mMRC dyspnoea grades, and ADO index scores, as there was little or no overlap between the 95% confidence intervals of the hourly patterns. The AUC-values for these parameters varied between 0.25 and 0.36 (Table S4 in File S2). The influence of GOLD grades or GOLD groups on these patterns was small. Moreover, only weak associations existed between FEV1 (% predicted) and the time in activities of very light, light, and moderate-to-vigorous intensities (Fig. 3).

**Fig. 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).** Figs. A, C, E, and G represent weekdays, while figs. B, D, F, and H represent weekend days. Data pooled per hour as mean (95% confidence intervals).

**Fig. 3.** **Spearman’s correlation between forced expiratory volume in the first second (% predicted) and the daily time in activities of very light intensity (A), light intensity (B), and moderate-to-vigorous intensity (C) for 1001 patients with chronic obstructive pulmonary disease.**

**Cluster Analysis of Daily Physical Activity Measures in 1001 Patients with COPD**

The PCA identified three components, which accounted for 60% of the total variance (first component, 34%; second component, 17%; third component, 9%). The most relevant features of each principal component are described in File S2. Cluster analysis, performed on the three principal components, identified five distinct clusters (Fig. 4; see S1 Video for a 3-dimensional video of Fig. 4). Table 3 presents the characteristics and physical activity measures of these groups. Cluster 1 (n=216, 22%) was characterized by higher BMI, more dyspnoea, 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. Cluster 2 (n=415, 41%) had more dyspnoea 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 (n=184, 18%) exhibited a higher FEV1 than cluster 2, while cluster 4 (n=165, 17%) 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, while cluster 4 spent more time in light intensity compared to cluster 5. Cluster 5 (n=21, 2%) was characterized by less time in very light intensity and more time in moderate-to-vigorous intensity compared to other clusters. Fig. 5 presents the daily time in activities of different intensities by the clusters, highlighting the mixed arrangements of physical activity. Fig. 6 presents the daily physical activity 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. Hourly patterns after synchronisation of the waking up moment are presented in S2 Fig. Moreover, increasing AUC-values were found from clusters 1 to 5 (S4 Table in File S2).

**Fig. 4. 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 File S2.

**Fig. 5. Daily time in activities of very light intensity (A), light intensity (B), and moderate-to-vigorous intensity (C) by clusters of patients with chronic obstructive pulmonary disease.** Data presented as median (interquartile range).

**Fig. 6. Daily physical activity hourly pattern of clusters of patients with chronic obstructive pulmonary disease during weekdays (A) and weekend days (B).** Data pooled per hour as mean (95% confidence intervals).

**Table 3. General characteristics and daily physical activity measures of clusters of patients with COPD.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic/Physical activity 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 |
| mMRC dyspnoea 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 ≥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 ≥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 ≥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 ≥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 ≥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 ≥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 ≥10-min bouts, min∙bout-1 | 12 (11 – 13) | 12 (11 – 14) | 14 (13 – 15)†,‡ | 12 (11 – 14)§ | 13 (11 – 14) | <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 ≥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 ≥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 ≥10-min bouts, min∙bout-1 | 14 (11 – 16) | 14 (12 – 15) | 14 (12 – 17) | 17 (15 – 21)†,‡,§ | 20 (17 – 25)†,‡,§ | <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. The description of the clusters presented at the top of the table was arbitrarily based on the amount of time in very light and moderate-to-vigorous intensities.

**Discussion**

The present study provides detailed analyses of objectively measured physical activity in a multinational sample of 1001 patients with COPD. The principal findings show that daily physical activity measures and hourly patterns vary considerably after stratification for generic and COPD-specific characteristics; and that patients with COPD can be clustered based on daily physical activity measures, with five clusters being identified, each with distinct physical activity measures and hourly patterns.

**Daily Physical Activity Measures and Physical Activity Hourly Patterns in COPD**

Our results clearly show that physical activity is a heterogeneous characteristic in patients with COPD, corroborating previous findings [30, 31]. Distinct levels of physical activity were found after stratification for age (< or ≥ 67 years), sex (male or female), BMI (underweight to obese), mMRC dyspnoea grade (0 to 4), LTOT (yes or no), DLCO (< or ≥ 51% predicted), ADO index (< or ≥ 4 points), GOLD grades (1 to 4) and GOLD groups (A to D) (S5-S13 Tables in File S2). Interestingly, comparable time in very light and moderate-to-vigorous intensities was found between GOLD groups A and C, and between GOLD groups B and D (S13 Table in File S2). This suggests that symptoms of dyspnoea, which discriminates between groups A/C and B/D, are better associated with physical activity measures than the degree of airflow limitation, which discriminates between groups A/B and C/D. Zogg et al [32] also investigated physical activity levels in COPD patients after classification into GOLD groups. These authors observed more preserved physical activity levels in group A compared to the other groups. Nevertheless, the sample size of each group was small and groups C and D had to be combined, compromising more detailed analyses. Despite the significant influence of GOLD groups on physical activity measures, only little or no influence was observed on physical activity hourly patterns. Only a few studies have investigated hourly patterns in COPD. In the study by Hecht et al [10], the authors observed that the highest activity level occurred during the late morning and early afternoon hours, which is corroborated by our findings. Tabak et al [33], in turn, observed a similar pattern of a dip of lower activity in the early afternoon in both employed and unemployed COPD patients, despite differences in the summary values between groups. Together with our findings this suggests that hourly patterns have the potential to complement the information provided by summary values.

**Clusters of Patients with COPD Based on Daily Physical Activity Measures**

The present study is the first to cluster patients with COPD based only on objectively assessed physical activity measures. Indeed, five clusters were identified, each with distinct physical activity measures and hourly patterns. One very active cluster and one very inactive cluster were identified, but clusters in intermediate categories were also observed.

Only a few studies have used objectively measured physical activity data solely for clustering subjects. In 10-to-12-year-old children, De Bourdeaudhuij and colleagues [34] were able to identify a cluster with a mixed arrangement of physical activity (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 [34]. Based on the amount of time in 10 minutes bouts of moderate-to-vigorous physical activity, patients from cluster 4 could be considered physically active [26]. Nonetheless, these patients spent over 11 hours in very light intensity (i.e., sedentary behaviour), and previous studies have shown the detrimental effects of prolonged periods of sedentary behaviour on health outcomes [35, 36]. More inactive clusters were also observed in our study (clusters 1, 2 and 3). In middle-aged Chinese adults, Lee et al [9] observed that male subjects from the least active cluster had higher body fat percentage and older age than those from the active group. In our study, patients from cluster 1 had older age, lower FEV1, higher BMI, worse dyspnoea 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 are available to confirm this hypothesis.

Although there was little or no overlap between the 95% confidence intervals of the hourly patterns of the clusters, confirming that they are statistically different, the patterns were found to be rather similar. Nevertheless, more inactive clusters seem to present less variability in intensity compared to more active clusters, suggesting that they are similarly inactive throughout the day. We also observed that the more inactive a cluster is, the more similar its hourly patterns of weekdays and weekend days are. This corroborates the findings from Lee et al [9], who observed a consistently low physical activity pattern on both weekdays and weekend days in the least active cluster. Irrespective of the cluster, patients seem to perform the activities with the highest intensity during the morning, which was also observed after stratification for different characteristics (Fig. 2 and S1 Fig.). This should be taken into account when planning interventions such as energy conservation techniques, which have as one of the main aims to reduce unnecessary energy expenditure associated with activities of daily living [37].

**Clinical Relevance**

Patients with COPD spent around 80% of their daily time in activities of very light intensity (Table 2). Previous intervention studies in COPD have focused on increasing the time in moderate-to-vigorous intensity [1, 8, 38], but there is emerging literature in other populations suggesting that health benefits can be achieved by decreasing time in very light intensity and increasing the participation in light intensity physical activities [18, 39-41].

Physical activity hourly patterns and physical activity clustering provide details on the duration and intensity of physical activities over the course of a day, as well as identify groups with specific physical activity patterns, which can broaden the understanding of physical activity in patients with COPD. Indeed, based on the results shown it can be speculated that cluster 1 is probably at increased risk of having a worse prognosis due to the combination of health-threatening characteristics (e.g., more time spent in very light intensity, less time in moderate-to-vigorous intensity). Moreover, identifying groups with specific physical activity patterns seems to be useful information for tailoring physical activity enhancing interventions. Cluster 1, for instance, spent a median of 15 min·day-1 only in moderate-to-vigorous intensity, which is half of the recommended by international guidelines [26], and more than 15 hours in very light intensity (i.e., sedentary behaviour), which is more than two times of what other studies have considered as harmful (i.e., 7 hours) [35, 36]. This cluster therefore, could benefit from an intervention focusing not only on increasing the amount of time in moderate-to-vigorous intensity, but also on reducing the time in very light intensity. Cluster 4, on the other hand, seems to spend enough time in moderate-to-vigorous intensity (i.e., >30 min·day-1 in 10-min bouts), but would probably benefit from an intervention aiming to reduce the time in very light intensity, which is over 11 hours. To date, interventions targeting physical activity enhancement had limited impact in patients with COPD [16, 38, 42], but none of these interventions targeted specific physical activity patterns.

Decreasing the time in very light intensity without necessarily increasing the time in moderate-to-vigorous intensity would mean focusing on light intensity activities. Reductions in sedentary time by increases in light activities might be more realistic for patients with COPD, which in fact could help pave the way to posterior increases in the time in more intense activities [18, 20]. This is supported by a recent study which demonstrated that greater quantity of low-intensity physical activity reduces the risk of COPD hospitalisation [19]. Of note, in that study high-intensity physical activity did not produce any risk reduction.

**Strengths and Methodological Considerations**

We have analysed a large and diverse sample of patients with COPD with objectively assessed physical activity data. This allowed detailed analyses of daily physical activity, even identifying clusters of patients with COPD with similar physical activity measures, a novelty within the COPD literature. Physical activity 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 physical activity.

Some methodological considerations need to be taken into account. First, selection and information biases might be present, as data were collected separately as part of different studies. Moreover, some types of patients with COPD might be underrepresented, such as patients from primary care. 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. Second, it was not possible to show whether the clusters identified in our study relate to relevant clinical outcomes, such as COPD-related hospitalisations and deaths due to the lack of follow-up assessments, or whether they could be replicated in another sample. Third, other characteristics which may influence physical activity levels in patients with COPD, such as comorbidities [43], were not available. Finally, some of our findings need to be interpreted in light of the number of multiple comparison tests performed. Nonetheless, multiple findings in the same direction rather than a single statistically significant result are suggestive that these are not due to chance alone.

**Conclusion**

To conclude, daily physical activity measures and hourly patterns in patients with COPD were found to vary considerably depending on the clinical characteristic and should be jointly assessed. Moreover, five clusters of patients were identified, each with distinct physical activity measures and hourly patterns. The present data show that outcome measures need to be clearly delineated when evaluating interventions aiming to promote physical activity in patients with COPD.

**Acknowledgements**

The Australian-based authors would like to thank the Pulmonary Rehabilitation Departments at Royal Prince Alfred Hospital (particularly Lissa Spencer), Concord Repatriation General Hospital, Prince of Wales Hospital (particularly Renae McNamara), Manly Hospital, Hornsby-Kuring-Gai Hospital, Sir Charles Gairdner Hospital (particularly Nola Cecins and Michelle Melang) and Bentley Hospital for assisting with participant recruitment.

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**Supporting Information**

**S1 Fig. Daily physical activity hourly patterns of the patients with chronic obstructive pulmonary disease after stratification for: A and B – age groups (< or ≥ median, 67 years); C and D – sex; E and F – long-term oxygen therapy (LTOT) use (yes or no), data available for 707 subjects only; G and H – diffusion capacity of the lung for carbon monoxide (DLCO) groups (< or ≥ median, 51% predicted), data available for 505 subjects; and I and J – age, dyspnoea, and airflow obstruction (ADO) index groups(< or ≥ median, 4 points).** Figs. A, C, E, G, and I represent weekdays, whilst figs. B, D, F, H, and J represent weekend days. Data pooled per hour as mean (95% confidence intervals).

(TIFF)

**S2 Fig. Daily physical activity hourly pattern of the clusters of patients with chronic obstructive pulmonary disease after synchronisation of the waking up moment during weekdays (A) and weekend days (B).** Hourly patterns were presented before and after synchronisation to overcome the problem of subjects with different waking up times. Data pooled per hour as mean (95% confidence intervals).

(TIFF)

**S1 Video. 3-dimensional video of the five clusters identified according to the three principal component analysis (PCA) components.**

(AVI)

**File S1 Supporting Materials and Methods.**

(DOC)

**File S2 Supporting Results.**

(DOC)