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Physical activity patterns and clusters in 1001 patients with COPD

PLOS ONE

Dear Mr. Mesquita,

Thank you for submitting your manuscript to PLOS ONE. After careful consideration, we feel that it has merit, but is not suitable for publication as it currently stands. Therefore, my decision is "Major Revision."

We invite you to submit a revised version of the manuscript that addresses the points below:

The reviewers identified significant concerns with this manuscript which are listed below in the reviewer comments. Please carefully address these comments. The issue of the Italian data was identified as a significant concern by more than one reviewers and must be addressed- although the data is collected as part of routine care it is essential we are reassured that all data collection and use was approved by the ethical standards in that country. The manuscript cannot be published without a clear statement that this was done.

We encourage you to submit your revision within forty-five days of the date of this decision.

When your files are ready, please submit your revision by logging on to http://pone.edmgr.com/ and following the Submissions Needing Revision link. Do not submit a revised manuscript as a new submission. Before uploading, you should proofread your manuscript very closely for mistakes and grammatical errors. Should your manuscript be accepted for publication, you may not have another chance to make corrections as we do not offer pre-publication proofs.

If you would like to make changes to your financial disclosure, please include your updated statement in your cover letter.

In addition, when submitting your revision please include the following items:

A rebuttal letter that responds to each point brought up by the academic editor and reviewer(s). This letter should be uploaded as a 'Response to Reviewers' file.

A clean revised manuscript as your 'Manuscript' file.

A marked-up copy of the changes made from the previous article file as a 'Revised Manuscript with Track Changes' file. This can be done using 'track changes' in programs such as MS Word and/or highlighting any changes in the new document.

For more information on how to upload your revised submission, see our video: http://blogs.plos.org/everyone/2011/05/10/how-to-submit-your-revised-manuscript/

If you choose not to submit a revision, please notify us.

Yours sincerely,

James D. Chalmers, PhD MBChB MRCP (UK)

Academic Editor

PLOS ONE

Journal requirements:

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1. Please ensure that your manuscript meets PLOS ONE’s style requirements, including those for file naming. The PLOS ONE style templates can be found at:

http://www.plosone.org/attachments/PLOSOne\_formatting\_sample\_main\_body.pdf and http://www.plosone.org/attachments/PLOSOne\_formatting\_sample\_title\_authors\_affiliations.pdf

2. Thank you for stating the following in the Competing Interests section: “I have read the journal's policy and the authors of this manuscript have the following competing interests: Dr. Henrik Watz currently serve is an Academic Editor for this journal. All other authors have declared that no competing interests exist.”

We note that one or more of the authors have an affiliation to the commercial funders of this research study : GlaxoSmithKline

a. Please provide an amended Funding Statement declaring this commercial affiliation, as well as a statement regarding the Role of Funders in your study. If the funding organization did not play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and only provided financial support in the form of authors' salaries and/or research materials, please review your statements relating to the author contributions, and ensure you have specifically and accurately indicated the role(s) that these authors had in your study. You can update author roles in the Author Contributions section of the online submission form.

Please also include the following statement within your amended Funding Statement.

“The funder provided support in the form of salaries for authors [insert relevant initials], but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the ‘author contributions’ section.”

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b. Please also provide an updated Competing Interests Statement declaring this commercial affiliation along with any other relevant declarations relating to employment, consultancy, patents, products in development, or marketed products, etc.

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Please include both an updated Funding Statement and Competing Interests Statement in your cover letter. We will change the online submission form on your behalf.

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3. We note that you stated “data are available upon request” at submission. Could you please confirm that all data underlying the findings in your study are freely available in the manuscript, supplemental files, or in a public repository? If this is not the case, and your data are available upon request because of an ethical or legal restriction or because you obtained data from a third party, please include the following in your revised cover letter:

a. The reason why your data cannot be made available in the manuscript, the supplemental files, or a public repository;

b. The name(s) of the individual(s) that readers may contact to request the data;

We will make changes to your data availability statement on your behalf, based on the information you provide. For more information about our data policy and acceptable reasons for not making your data fully available, please refer to: http://www.plosone.org/static/policies#sharing

**Reviewers' comments:**  
  
Reviewer's Responses to Questions  
  
**Comments to the Author**  
  
1. Is the manuscript technically sound, and do the data support the conclusions?  
  
The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.   
  
Reviewer #1: Partly  
Reviewer #2: Yes  
Reviewer #3: Partly  
Reviewer #4: Yes

2. Has the statistical analysis been performed appropriately and rigorously?   
  
Reviewer #1: Yes  
Reviewer #2: No  
Reviewer #3: I Don't Know  
Reviewer #4: Yes

3. Does the manuscript adhere to the PLOS Data Policy?  
  
Authors must follow the [PLOS Data policy](http://journals.plos.org/plosone/s/data-availability), which requires authors to make all data underlying the findings described in their manuscript fully available without restriction. Please refer to the author’s Data Availability Statement in the manuscript. All data and related metadata must be deposited in an appropriate public repository, unless already provided as part of the submitted article or supporting information. If there are restrictions on the ability of authors to publicly share data—e.g. privacy or use of data from a third party—these reasons must be specified.  
  
Reviewer #1: Yes  
  
Reviewer #2: Yes  
  
Reviewer #3: Yes  
  
Reviewer #4: Yes

4. Is the manuscript presented in an intelligible fashion and written in standard English?  
  
PLOS ONE does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors here.  
  
Reviewer #1: Yes  
  
Reviewer #2: No  
  
Reviewer #3: No  
  
Reviewer #4: Yes

5. Review Comments to the Author  
  
Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)  
  
Reviewer #1: This is a cross-sectional analysis of physical activity patterns from a large multi-national dataset of over 1000 patients with COPD. Cluster analysis has been used and identified distinct cluster phenotypes related to physical activity patterns.  
  
Overall this is well written, presenting novel findings and technically sound, other than a couple of points below.  
  
Comments:  
  
1) 5 clusters were identified in the analysis. I am unsure how valid cluster 5 is compared with the others. Cluster 5 contains only 21 (2%) of patients. Looking at the figure, it may be that many of these patients would fit in cluster 4 but have been skewed by some outliers.  
  
2) One of the big advantages of this study are the large number of patients involved. It seems odd to also include a comparison with only 66 matched healthy volunteers. I do not think this adds to the manuscript.  
  
3) The area under the curve results are presented as negative predictors (i.e. AUROC <0.5). This is unusual and would normally be presented as positive predictors.  
  
Reviewer #2: General  
The strength of the paper is that it involves a cohort of 1,001 patients.   
  
However, the findings are not novel from what has already been previously reported in smaller cohorts. It is disappointing that such a large cohort was not used to provide information about differences in PA and its patterns between the 10 countries. We do not know what norms are for various geographical regions, and this cohort could potentially provide this needed information.  
  
The clinical significance of the clusters is unclear as they are not associated with any clinical characteristics or outcomes such as acute exacerbations, COPD-related hospitalizations, or death. Are these phenotypes of the heterogenous COPD population?  
  
There is an overwhelming abundance of data being presented, particularly in the Tables and Figures. Please focus the main messages to be conveyed and simplify the Tables and Figures.  
  
Abstract  
What specifically is “insufficiently understood” about physical activity in COPD?  
  
It is unclear how the clusters would be useful for PA interventions. How should PA interventions target PA patterns?  
  
Introduction  
Why is it important to understand hourly patterns and temporal patterns? What is the hypothesis being entertained about temporal patterns—that it is better than summary values, intensity, or bouts? It seems the patterns are dictated more by human behavior (more active in morning/around lunch time, and less active in the afternoon as we settle down from a busy day and relax for the evening) than by COPD or its severity.  
  
Reference 17 should be replaced or supplemented by the recent ERJ paper looking at the association between low-intensity PA and risk of COPD-hospitalization.  
  
Methods  
I raise concern whether it is ethical to include the 23 patients from Italy who did not give written informed consent. De-identification is important to protecting patient information and confidentiality, but this does not mean clinical data can be used for research purposes without consent.  
  
What is the median split method? Please provide a reference.  
  
How was clinical stability at the time of PA assessment defined? How long since the last acute exacerbation or hospitalization was the PA monitored?  
  
Was the diagnosis of COPD based on the FEV1/FVC ratio alone? Is there possibility of misclassification of asthma for COPD?  
  
After discussing how PA should not be represented by summary data, the PA measures in this study represent “the average” of all valid weekdays. Please discuss.  
  
What are the units to PA being used, if not steps per day?  
  
The aims stated in the last paragraph of the Introduction do not include anything on PA intensity, but the methods and results discuss PA intensity in great detail. Please clarify. There is also no aim on PA bouts, but the results seem to focus on bouts. Please explain what are physical activity measures. There is also no discussion of GOLD stage but these are presented extensively in the Figures.  
  
Healthy subjects were matched in age, gender, and BMI. Were they healthy because they did not have COPD or because they had no comorbidities? Matching on comorbidities, such as CAD, PVD, back pain, that affect PA would be important. Were healthy subjects retired or employed? What were their demographics? These factors all affect PA.   
  
Why do models not adjust for site of study?  
  
Results  
The description of the clusters in Table 4 need full explanation in the text. What is very long, very light intensity? What is the difference between very long versus long; very short versus short?  
  
What does stratification of results by age, gender, and LTOT, DLCO, and ADO add to the overall results?  
  
Figure 2. The authors state Figure 2 shows a “noticeable influence of age, BMI, mMRC, and ADO.” Was there any statistical methods applied to prove that there is a difference between the curves?  
  
Figure 3 has been previously shown many times. It is not presenting anything novel.  
  
Please discuss that Figure 4 shows no difference between COPD and healthy with respect to the pattern of PA over hours of the day. This was a main aim of this paper.  
  
Please present the results of the 3 components in the main paper rather than in Supplement File 2 since this is a main aim of the paper.  
  
Figure 6 looks strikingly very similar to Figures 1 and 2 in terms of hourly patterns. What additional information does Figure 6 provide?   
  
The issue of synchronization of the waking up moment is first presented in the Figure 6 legend. What is its significance? It should be discussed in the methods and results.  
  
Reviewer #3: The authors present a manuscript that describes physical activity patterns in those with vary severity of COPD and some healthy controls. The manuscript presents an enormous data set with many comparisons being made.  
  
I am the first to appreciate all data being presented, but, in this case, the extreme amount makes the manuscript difficult to read and nearly impossible interpret. I was often lost at what comparison was being made and very few were actually justified in the introduction and/or elucidated in the discussion. Rather, the discussion was vague and did not address specific finding, presumably because there were too many. As such, I was lost as to what data was being referenced to justify which conclusion. I note PLOS ONE does not have a word limit, as such, I am lost as to why the discussion so vague, short and poorly developed?  
  
There was a discrepancy between the sexes for this study. There are many well know sex difference in the respiratory system and many specific to COPD. This was not stated at all in the manuscript and needs at least to be mentioned.  
  
Different countries were shown to have different physical activity levels, however, the control group was only from two specific countries. As such, how can the comparisons between the controls be justified to the COPD cohort.  
  
There are a lot of statistical comparison but the specific analytical techniques were not as well described I they could be. For example, how were multiple comparisons handled? Clearly there were many instances.  
  
The methodological considerations were not complete and many of the problems were not fully elucidated. For example, “ Second, the clusters identified in our study were not validated”. Not further explanation was provided. What does this mean? How could it affect the results? Did it alter the results?  
  
Many conclusions are not justified or even explained. Specifically, how could the results help promote physical activity in COPD?  
  
I note on their website PLOS ONE specifies:  
“PLOS ONE editorial decisions do not rely on perceived significance or impact, so authors should avoid overstating their conclusions”  
Throughout the manuscript there are many occasions where the authors both overstate their conclusion and do so without sufficient evidence to justify their conclusion. Often mention words being the “largest” “biggest, multicentered”, such remarks appear to be highlighting novelty and interest, which I believe is not necessary in this journal. Also, the data is all part of larger studies and while I do not believe the specific results may have been reported elsewhere, this ends up being in a “grey” zone of publishing ethics.  
  
Reviewer #4: Review attached  
  
Physical activity patterns and clusters in 1001 patients with COPD   
  
This is a large data set of daily physical activity data in COPD collated from multiple previous trials. Describing the overall pattern of physical activity is helpful and the principle of performing cluster analysis is novel in this area (certainly in a large sample size). Although the authors should be congratulated in co-ordinating the data collection, there are some inherent bias’ and limitations in the data which need further discussion. The clusters overall appear to describe a range of different levels of physical activity rather than different patterns (Figure 5) – the daily patterns seem rather similar except the variability seems to diminish as people are more inactive. The figures presumably would be published in colour as perhaps some of the detail in the figures does not ‘shine’ through, but if so it is even more important to highlight any novelty of these clusters in the text. Is the main finding that the least active and sedentary cluster are obese, more breathless with more severe disease? The limiting factor is the limited number of variables available due to the study design.   
  
The construct of physical activity is complicated and the health outcomes are discussed in a rather simplistic and generalised way. It is likely that sedentary behaviour is associated with different health outcomes to intense bouts of exercise which shouldn’t diminish the importance of either -suggest adding something to this effect in the discussion. The authors include many world renowned experts in this area and as such their ‘voice’ is likely to be far reaching. It is therefore essential that only messages directly from the data are discussed. There is no evidence from the data to suggest the current advice around intensity of activity/exercise should be altered even if there may need to be additional advice around not being sedentary. Please rephrase the comments under clinical relevance and at the bottom of Pg 6 Intro; ‘The focus may be shifted …’ Understanding the patterns of outcome would not be enough to change the focus of activity/exercise interventions – understanding the difference in outcome might do but this is likely to vary between patients and should not be a ‘global’ message.   
Major comments  
1) By nature this analysis is retrospective and therefore suffers the usual weaknesses. It needs to be described as such in the study design. There is no mention on how many patients have been excluded and whether they had similar characteristics to the population described (the large dataset does not obviate this) which is potential for systematic bias.   
2) How was it decided who would contribute to the dataset? Were all authors of studies involving physical activity and COPD in a certain time frame using sensewear monitors contacted? Bias could have been introduced if this wasn’t systematically approached. (perhaps this data is in the supplementary files but if not please add to the methods)   
3) The data is cross-sectional so provides no insight into how these clusters relate to health outcomes – this needs adding to the limitations.   
4) As the authors state the clusters haven’t been validated in a further population.  
5) Presumably resting energy expenditure was not taken into consideration?   
6) Presumably the same formulae for extrapolating energy expenditure were used? Are these the same between the Sensewear and Mini-sensewear?  
7) The authors need to comment somewhere that these levels are all at an absolute level. Relative to their peak exercise capacity these people will be active at a much higher relative intensity – it is not fully understood whether this might still have health benefits which needs comment.   
8) Suggest removing FEV1/FVC as a comparator variable across the clusters as this is a descriptor only.   
9) The abstract is rather vague more precision is needed in the results about what the associations are between the variables. Please describe ‘cluster 1’ otherwise it does not make sense when reading the abstract alone.   
10) Although there has been evidence (from some of the authors) that there are differences between weekday and weekend activity, is that supported in this large dataset? The patterns look rather similar in all the figures. Was there a statistical difference in the volume of activity or the pattern of activity between the weekend and weekday in any of the data. If not it might be better to combine this data for the cluster analysis?  
11) Interesting the hourly pattern of activity looked rather similar for healthy and COPD participants – is this what was expected?   
12) As the authors mention, a major limitation is that few patients had mild –moderate COPD.   
13) Did the ‘italian’ patients agree to have their data stored and used for research purposes even if ethics permission wasn’t needed to collect the data  
  
Minor comments  
1) References 11,12 are in children – suggest adding ‘In other population, …’ at the start of the first paragraph so that the reader knows this is not referring to patients with COPD.   
2) Ref 14 isn’t a reference about physical activity but phenotyping – move the ref to after ‘cluster analysis [14] …’ – suggest changing the phrasing of ‘cluster analysis will be …’ to ‘could be’  
3) Intro Pg 6 following line from above change ‘will then’ to ‘could then lead …’  
4) Table 1 the numbers don’t seem to add up for the BMI classifications (only around 100 patients in total?) nor for the GOLD classifications. Probably don’t need both GOLD classifications, similarly probably don’t need height and weight to be described.   
5) Results. The initial description is not necessary as the results are in Table 1. If left in please add ‘The majority’ and remove ‘ GOLD stage D …’ as this is a bit misleading as there was reasonable split across the GOLD stages in the small number described.   
6) Pg 12 line 224 add ‘total’ to ‘time and lowest energy expenditure’ and same Pg 13 line 247  
7) Remove comment regarding FEV1/FVC line 299

6. If you would like your identity to be revealed to the authors, please include your name here (optional).  
  
Your name and review will not be published with the manuscript.   
  
Reviewer #1: (No Response)  
Reviewer #2: (No Response)  
Reviewer #3: (No Response)  
Reviewer #4: No  
  
[NOTE: If reviewer comments were submitted as an attachment file, they will be attached to this email and accessible via the submission site. Please log into your account, locate the manuscript record, and check for the action link "View Attachments". If this link does not appear, there are no attachment files to be viewed.]