Dear Mr. Mesquita:

I write you in regards to manuscript # thoraxjnl-2014-206701 entitled "Physical activity patterns and clusters in 1001 patients with chronic obstructive pulmonary disease" which you submitted to Thorax.

We receive many more manuscripts than we can publish. In view of the comments of the reviewers found at the bottom of this letter, your manuscript has not reached a high enough priority for publication in Thorax. We are sorry to disappoint you, and hope that nonetheless the comments are of value to you as you move forward with the work.

We commend you for putting together such a large dataset and bringing investigators from all across the world to tackle this important question. However, in our opinion, the study was largely descriptive and the findings were mostly expected. The study would have been strengthened by having longitudinal health outcomes data to validate the importance of the clusters that you determined in the study.

Thank you for considering Thorax for the publication of your research. We hope the outcome of this specific submission will not discourage you from the submission of future manuscripts.

Sincerely,

Professor Andrew Bush

Editor-in-Chief, Thorax

Professor Ian Pavord

Editor-in-Chief, Thorax

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

Physical activity patterns and clusters in 1001 patients with chronic obstructive pulmonary disease.

General view of the article

- Currently a very important topic in COPD.

- Some of the authors are well-known people in this area of physical activity and COPD. We could say that the most important researchers on this topic are contributors in the article.

- Well-presented material.

- Plentiful, clarifying online material

Objective:

The way the authors focus on the topic (objectives) seems suitable and contributes to the general knowledge of physical activity in COPD patients.

Methods

- A very important question is how these COPD patients were recruited. They had participated in different studies with different objectives and different methodologies. We can see that there are two main groups of studies, inhaled medication clinical trials and rehabilitation studies. So these patients would have specific characteristics in relation to these studies (inclusion criteria) and this probably could have influenced on the quantity and characteristics of the physical activity. In other words, the different selection criteria of patients could have an impact on the results.

Gab: Differentiate between inhaled medication clinical trials and rehabilitation studies. Run stratification according to this criteria.

On the other hand, we do not have any information about the COPD patients that were excluded in those studies, neither about the missing data. Authors only make a brief reference to this question but I think they have to be more emphatic and clarifying in this point.

Gab: Rafael? Can you write more/answer to the reviewer question?

The reader should not have any doubt about the importance of the results.

Gab: I would omit pag. X line x.

- The second main question (we must say it is mentioned by the authors) is the absence of data related to comorbidities. Comorbidities, especially heart diseases, can almost certainly, outline these clusters more precisely, and even become the key factor in some of them. The lack of this data seems to be relevant.

Gab: we cannot do much for this.

- It is necessary to define “stable condition” and if this criterion was identical in every study included in the article.

Edit the text saying for example that stable condition is:

Statistical Analyses:

- Clear, concise and correct.

Results and Discussion:

- A considerable number of patients studied.

- The results are interesting from a general point of view. It seems that the behaviour of COPD patients with respect to the general population is not so different but at a lower level of activity. In any case comparing 66 people does not seem to be sufficient in order to establish that conclusion.

Gab: the main conclusion shouldn’t be the importance of taking into consideration low level physical activities.

- I am not sure if a cluster with 21 patients actually can establish a subtype of patient. (minor)

Gab: we do not want to define new phenotype of patients..

- It is disappointing to observe that the clusters described were not associated with relevant outcomes.

Gab: the cluster described should be described with the associated clinical outcomes (FEV1 etc..)

Personal opinion:

Very interesting article on an interesting topic, but I am concerned about how the different cohorts have been joined together, the likely impact of comorbidities that has not been considered and the lack of outcomes that in some way validate these clusters. This article certainly will be reference in many others focused in this topic.

Reviewer: 2

Comments to the Author

COPD patients have been found to be less physically active compared to controls, and population-level data has shown that physical (in)activity is associated with mortality and hospitalizations in COPD. Thus, there is a rapidly developing literature examining physical activity (PA) and health outcomes in COPD. Population-based studies have used self-report PA (notoriously unreliable), while the studies to-date that have used objectively measured PA have been generally of moderate size (n=~100), and have typically summarized the data in units such as daily step count, and compared patients across disease severity (i.e. FEV1). Thus, there is a need for larger studies of PA in COPD using more precise methods of PA determination.

The current study examined physical activity patterns and clusters in a large (n=1001) sample of COPD patients. As one would expect, the current study found that COPD patients were less active and performed less moderate-to-vigorous PA than controls, and COPD patients who were old, had more dyspnea and more severe GOLD performed less moderate-to-severe PA as compared to milder COPD. Importantly however, PA and hourly patterns varied considerably after stratification for generic and COPD-specific characteristics, and the authors were able to identify 5 patient clusters of PA patterns within the COPD cohort.

The study is well executed, and the paper well written. The sheer volume of objectively measured PA data spanning multiple centres and countries is impressive. Further, the pairwise matching of COPD and controls for age, sex and BMI is a strength over previous work. While some of the basic findings are somewhat intuitive, the documentation of significant heterogeneity in PA and the identification of patient clustering is important as we look for interventions to modify PA in these patients.

Critique

While this reviewer agrees with the authors that a more detailed analysis of PA patterns is needed in COPD, I found that the rationale detailed within the introduction could be stronger. The authors briefly discuss cluster analysis, which is likely important; however, to the more general clinician the importance of this analysis may not be apparent. As an example, there is an ongoing debate in the PA research as to whether accumulated vs. continuous exercise training provides the ideal health benefit (see Murphy et al1 for recent review). The authors should better develop the clinical importance for a more detailed PA analysis in COPD. Likewise, consider moving your ‘clinical relevance’ section within the discussion further forward.

It is unclear why the authors did not also report step count. The Sensewear devices allow for determination of step count, and daily step count is being used for patient monitoring as it is an easy outcome that can be tracked by patients and clinicians. While daily step count does not provide information about clustering of PA, step-count data from this large multi-centre trial may be illuminating particularly for Table 4.

Gab: include step count in the analysis.

Exercise intensity was quantified using METS as detailed by ACSM. This is likely the best available approach to quantify intensity; however, it is worth noting in the limitations section that these cut-offs do not take into consideration the individual patient’s peak METS, which likely varies considerably across the cohort of COPD patients.

Gab: include max METS peak as a feature?

Along the same line, it is unfortunate that 6MWD data is not also reported and analyzed relative to PA.

Minor

Please provide data regarding the sample size obtained from each country.

Gab: provide sample size from each country.

Also, as PA levels have been shown to vary across country/continent, did you find any evidence of this?

Gab: stratify according to region/area.

Finally, were Belgian or Canadian data included? I note Belgian and Canadian authors, but neither country is listed in the methods as having recruited patients.

Gab: Belgium not Canada yes.

In describing your COPD sample, were any undergoing rehab (or any other type of intervention that could have affected their PA levels) at the time of measurement?

Gab: we do not know.

Page 14, line 44: I do not understand how COPD patients could spend a median of 6 minutes doing an exercise bout of >10minutes. I think your >2 and >10 values are flipped in this sentence.

Gab: it could be…

References

1. Murphy MH, Blair SN, Murtagh EM. Accumulated versus continuous exercise for health benefit: A review of empirical studies. Sports Med. 2009;39:29-43

Reviewer: 3

Comments to the Author

This study merges data from several studies that investigated physical activity (PA) in patients with COPD using one of two activity monitors from one company (BodyMedia). It strength is the size of the sample (just over 1000 patients included). The paper is generally well written, but the presentation of the data is complex with much reference to the online supplement, which complicates the reading. Although the study does bring together data from several regions world wide the authors do not (as far as I can see) use region, or season and or any other study related characteristic in their analysis (e.g. patients referred for pharmacologic study, rehabilitation, prior rehabilitation, etc...). This is unfortunate as it would perhaps make the data more interesting and innovative.

Gab: stratify according region, season, pharmacologic intervention, rehabilitation,

Since the study compiles data reported previously in literature and hence to some extend (e.g. patients with COPD are inactive) mainly confirms messages that were already common knowledge. Other parts of the data presentation (e.g. the diurnal pattern of PA) has been described earlier, but sometimes references to this earlier work are not given. For example, Hecht et al COPD 2009 and De Meyer et al Chest 2013 also described the hourly profile of physical activity in COPD patients. Comparison of COPD patients with controls was also done previously and systematic reviews on the topic exist. Obviously the present database is much larger, but seems to broadly confirm previously described patterns. Some discussion could be provided.

Gab: include references and say what our paper add to the current literature.

Although the study is large (1001 patients) the sample may still not be representative of COPD beyond patients typically seen in University Hospital clinics or –judging by the author names- rehabilitation facilities. There is some mentioning in the discussion but perhaps somewhat more insight in the types of patients likely underrepresented could be provided.

Gab: include reviewer request.

I’m missing an analysis of confounders such as geographical are or the influence of the moment of the year where patients were assessed. For example if a patient was assessed during Winter in a more ‘Nordic’ country, this could significantly influence the PA profile. Also the monitor that was used (2 different types seem to be allowed) could have influenced the analysis.

Gab: already asked by other reviewers.

The comparison of 66 COPD patients to matched controls does not add much, in my opinion. Were these subjects randomly selected from the data-base to match the healthy controls, or was there also a geographical and seasonal matching?

Gab: add this info.

The innovative aspect is in the cluster analysis of the PA data. Unfortunately, the clinical meaning of the 5 clusters of patients with distinct patterns remains unclear. Some follow-up of these patients could have shed light on which of these phenotypes is less desired than others. Perhaps more importantly, knowledge on the stability of a patient in a cluster might be important before the clinical relevance of the cluster is further discussed.

Gab: assess stability of a patient within a cluster. How to define?

Are test-retest data in some of these patients available? In addition it is not known to what extent these clusters of PA patterns also reflect clusters that would be present in the non-COPD population. Would all healthy for example cluster in 1 and the same cluster? Healthy subjects recruited in the different regions would clearly have been an asset to the interpretation.

Gab: Include Healthy in cluster analysis.

Similarly, could the authors provide insight in the stability of the hourly patterns. Are these stable within a patient?

Gab: stability of hourly pattern (provide with SD).

Much information is provided in the on-line supplement. This makes reading of the paper uncomfortable as one has to consult often the supplement for full understanding.

Specific points:

Why were weekends excluded from the cluster. I can envisage (looking at myself) that some patients may be characterized by having particularly active or passive weekends (compared to their weekdays). This may be the case in professionally active patients.

It might be useful to limit the factor analysis to items that are not too much directly depending one from the other.

Perhaps I missed it, but how was a ‘bout’ defined? In General I’m not sure how important this analysis is. Recent data from NHANES suggest that total rather than ‘bouted’ activity levels are of clinical relevance, when PA is truly measured. (Wolff J Phys act health 2014).

Gab: define bouts. Explain why we should consider bouts instead of total activity level. Add analysis total vs bouts.

Principle component analysis was limited to 3 factors as this allows visual display. Are there statistical arguments that 2 or 4 factors are not better (i.e. explain respectively much less (2 factorss) and not more (4 factors)) variance?

Gab: do this.

If you elected during submission to send your article on to another journal the article will be transferred in 5 working days. If you intend to rebut this decision please notify us before then.

The journal(s) (if any) you have selected at submission are:

If you want to speed up or stop this onward transmission please email the editorial office: thorax@bmj.com