Author's response to reviews

Title: Daily activity during stability and exacerbation of Chronic Obstructive Pulmonary Disease

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Author's response to reviews: see over
Dear Professor Budweiser

Thank you for considering our paper. We are very grateful to the expert reviewers for their efforts. We have responded to all their comments, and our modifications to the manuscript are described below.

The manuscript has been formatted to conform with instructions to authors, and a section on competing interests added.

With kindest regards

Ayedh AlAhmari
Gavin Donaldson

Reviewer 1

We are extremely grateful for your comments and criticisms which we hope have led to a significant improvement in the manuscript, and appreciate the time committed to the review.

General Comments

The rationale and justification for the study need more detailed development in the introduction.

The introduction has been extensively rewritten to give a description of the rationale for the study.

Why it is important to know what happens to daily activity around the time of an exacerbation?

See above about rewrite

Similarly, what is novel in this paper compared to what is already published is unclear.

See above about rewrite

The use of a pedometer in COPD appears to be novel and is brought up a few times through the paper, but there is little attention given to the pedometer. Was it worn with a validated device for comparison?

A pedometer is not novel. As the reviewer correctly points out – the novelty lies in its application in a cohort of COPD patients, which is why we carefully reported the reasons why data were not collected on all potential candidates.

The decrease in activity at exacerbation is probably overestimated. How do we know subjects didn’t feel well so stayed in bed and didn’t wear the pedometer for the full day and then forgot to wear it when got out of bed, rather than that they wore it for the full day but was not active?

The review is correct in that we cannot tell whether the patient was wearing the device for the whole day or not. Following the comment, we don’t think it likely that patients wore the pedometer less during their exacerbation. Our patients tend to adhere to the study protocol during exacerbation as we seen them in clinic at this time and remind them.
In my opinion the greatest value of this study is that one can monitor persons with COPD and track exacerbations prospectively. This has huge implications for early detection and early treatment of exacerbations. From your rich data in the community, is there any combination off step counts and symptoms that would alert when the patient should contact his provider now rather than waiting?

We did not look for this but early objective identification of an exacerbation is the holy-grail in COPD. Figure 2A suggests that step-counts would be too variable a measure.

Overall, the conclusions were overstated based on the results. These are associations found in an observational study in analyses that did not adjust for any possible confounders. Even the strength of association of 0.56 for the relationship between change in step count and recovery time is moderate at best.

Most of comparisons are before and during recovery of the same exacerbation. This self-case controlled approach does not really require adjustment for confounding. Investigation of whether changes at exacerbation were greater or smaller in particular sub-groups e.g., GOLD I-II verses GOLD III-IV would only add to the complexity of the paper.

Abstract

Intro-rationale for study is unclear

The reviewers comment is very helpful and we have modified the abstract to hopefully make our rational clear. It now reads “During most COPD exacerbations, patients continue to live in the community but there is little information on changes in activity during exacerbations due to the difficulties of obtaining recent, prospective baseline data.”

Methods-for how long were subjects followed?

We have modified the abstract to say that “They recorded pedometer data on a median of 198 days (IQR 134-353).

Results: how many of the 73 subjects were frequent exacerbators versus infrequent exacerbators?

We have rewritten the results to make the numbers clear. It now reads “Daily step count fell faster over time in the 40 frequent exacerbators, by 708 steps/year, compared to 338 steps/year in the 33 infrequent exacerbators (p=0.002).

Conclusion-it is unclear how the results support the conclusion that frequent exacerbators should be targeted for exercise programs. COPD exacerbations reduced physical activity—I am not sure you have shown this cause and effect. You have shown that frequent exacerbators have an associated reduction in physical activity.

We take the reviewers point and have removed this from the abstract. We now say that “COPD exacerbations reduced physical activity and frequent exacerbations accelerate decline in activity over time”.
Introduction

1. First 2 paragraphs. There seems to be general summary of COPD. A more focused look at physical activity monitoring in COPD and exacerbations is needed.

   The introduction has been extensively rewritten to give a rationale for the study.

2. Again, the rationale for the study is unclear

   The introduction has been extensively rewritten to give a rationale for the study.

3. How are frequent exacerbations ‘a stable feature’ of the disease when half your cohort did not experience an exacerbation?

   The phrase ‘a stable feature’ comes from the Hurst et al NEJM paper which showed that patient have a similar exacerbation frequency, whether they had 0-1 or >=2 per year. About 45% of the Eclipse cohort had no exacerbations in the 1st year of observation, which is possibly why it is so stable.

4. The second paragraph about pulmonary rehabilitation is distracting and it is unclear how it contributes to the overall rationale of paper.

   We agree with the reviewer that the 2nd paragraph is unfocused and have replaced it. Though, we still refer to pulmonary rehabilitation as maintaining physical activity during exacerbation may prevent the faster decline in patients with frequent exacerbations.

5. The third paragraph talks about pedometer versus accelerometer. Is this the point of the paper?

   We have previously been criticized for not using an accelerometer but this was not feasible in terms of patient attendance at clinic and the costs of 199 accelerometers.

Methods

1. Were subjects enriched (on oxygen, had an exac the year prior to study entry) to have an exacerbation during the study?

   Our cohort was not enriched as we wished to report on patients typical of those in general practice.

2. Time since last exacerbation should be reported.

   We have added to the results “The median time since the last exacerbation was 85.5 days (IQR 42-193). The shortest interval was 15 days. There was no record of the preceding exacerbation for 7 exacerbations as these patients had been recently recruited.”
3. Please provide reference for your definition of an exacerbation. It seems that your definition could easily misclassify the normal daily variation of COPD (due to secretions, air quality, humidity etc) as an exacerbation.

Our definition is well known as we have consistently used it since 1995. It has been validated against quality of life (SGRQ, CAT scores), lung function decline, change in inflammatory markers. Two references already cited have been added. If the reviewer would like we could add more references but perhaps too much self-citation should be avoided.

4. Is there any validation of the use of this pedometer in the COPD population?

The Yamax Digiwalker SW-200 has undergone validation and been used in clinical trials with COPD patients. We have added to the text “This pedometer has been shown to accurately measure steps in free-living individuals (22) and in normal and moderately obese patients (23) and detected differences in physical activity of COPD patients recorded their daily step count on the diary cards.

5. The division of subjects into frequent and nonfrequent exacerbators is unclear. Was this based on number of exacs prior to study entry or number of exacs found during the 19 month of follow-up?

We did mention in the abstract that division of patients into frequent and infrequent exacerbators was based on the 12 months preceding the start of the study. We now include this in the methods as well. It now reads “Patients were then divided into two groups, based on the number of exacerbations in the 12 months preceding the start of the study, those with 2 or more exacerbations per year were called frequent exacerbators and those with 0 or 1 exacerbation per year called infrequent exacerbators (25)”.

6. What are ‘changes in exacerbations’ on page 6?

Our apologies for being unclear. The sentence now reads “Changes at exacerbations in daily step-count, symptoms count, PEF and hours spent outdoors were assessed by comparison of the average over a 7 day baseline period which started 2 weeks before onset with the average over a 7 days exacerbation period starting on the day of onset”.

7. How were exacs handled if they occurred close together in time-- were exacs counted as the same exac or 2 different exacs?

A second exacerbation could only be indentified when there had been five consecutive days free of all recorded symptoms (24)

8. Definition of recovery requires more explanation

We have added that “ A moving average was used to avoid false early recoveries when step count or lung function improved for just a single day, but then remained below baseline for a few more days (6). We have also added a reference where we first used this approach to assess recovery.
9. The definitions of baseline, stable, and change and how the values for these time periods were derived from the daily step counts need to be made clearly.

These time periods were not derived from the daily step count but used in assessing and quantifying the daily step count and other parameters. The definitions have been made clearly – see above.

Results

In general, the results are not novel and are completely expected.

These results are as you might expect but there is no previous prospective data relating recovery in physical activity coupled with data on recovery of symptoms, PEF or time outside the home.

Were step counts recorded for 17,161 days or for 14,653 days?

Patients recorded step counts for 17,161 days. 14,653 days refers to the number of days when the patients were stable. A stable step count was defined as outside a period starting 2 weeks before and ending 2 weeks after an exacerbation. We have added data on the number of days during the exacerbation state/period to make the distinction clearer.

It is unclear when the entire cohort is analyzed and presented and when only a subset is being presented.

The data were subgrouped in many ways and this was confusing. Treated versus untreated. Frequent exacerbators versus infrequent exacerbators. Aren’t these both markers of severity?

There were only two sub-group analyses which are not excessive. Treated versus untreated exacerbations and between frequent and infrequent exacerbators both are important markers/phenotypes. We feel that the reviewer/editor would wish to see these data if left out.

Isn’t treated and untreated a marker of the severity of the exac? It is not surprising that untreated exacs which are milder would have a smaller decline in activity and a faster recovery.

Yes, but it also says something about why some patient seek medical help about their exacerbations and other do not. Patient seeks help if their normal activities are impaired. Unreported exacerbations are important as patient who reports a smaller percentage of their exacerbations have a poor quality of life (Wilkinson et al AJRCCM 2004).

Discussion:

Are the differences in step counts (370 steps per day) clinically important?

Daily step count fell by 480 steps per day between baseline and exacerbation. As yet there is no minimum clinically important difference of daily step count in COPD. We hope that this paper will add to the literature on which such an expert-lead decision can be made.
References:

Would discuss in context of Waschki paper on step counts predicting mortality and Moy PLOS One paper on step counts predicting exacerbations.

Both papers are referred to in the introduction.

Legends:

Would put n values for each figure.

We now refer to numbers in the figure legends where they will be more easily understood except for figure 4 where they are included in the figure.

Fig 1. What are the predicted values?

The predicted values were calculated from the equation derived from the random effects, linear regression model. We have revised the figure legend to read “Figure 1: Daily step-count of 33 infrequent (number of days with data=6878) and 40 frequent (number of days with data=7775) exacerbators; predicted values obtained from the random effects, linear regression model (test of interaction, p=0.002).”

Table 1.

Do you know how many participated in prior pulm rehab, how many participate in regular exercise?

22 (59.5%) of the 37 patients had participated in prior rehab. We have no data on whether they continued to participate in regular exercise.

Figure 1. Is time 0 study entry?

The figure legend now includes “Time 0 corresponds to the start of the study”.

Figure 2. What are n’s? The definitions of baseline, stable, and change and how the values for these time periods were derived from the daily step counts need to be made clearly.

In the methods, we define baseline as a “7 day baseline period which started 2 weeks before onset”. Changes are the difference between baseline and “the average over a 7 days exacerbation period starting on the day of onset”. These time periods were not derived from the daily step counts. The baseline was defined, as in our previous study (6). The 7 day onset period was a chosen as it avoids any day of week effect on activity.

We have specified the number of exacerbations in the figure legend.

Figure 3. What are n’s?

We have specified the number of exacerbations in the figure legend.
Reviewer's report

Title: Daily activity during stability and exacerbation of Chronic Obstructive Pulmonary Disease

Version: 3 Date: 16 April 2014

Reviewer: Henrik Watz

Reviewer’s report:

Alahmari et al studied the effects of exacerbations on daily step counts.

The study is of clinical interest. Methods and results are sound.

I don't have further comments.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.