Author’s response to reviews

Title: Risk of Acute Exacerbations in Chronic Obstructive Pulmonary Disease Associated with Biomass Smoke Compared with Tobacco Smoke

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Author’s response to reviews:

March 1, 2019

Dear Alice Turner

We are pleased to resubmit the revision of our manuscript, entitled “Risk of Acute Exacerbations in Chronic Obstructive Pulmonary Disease Associated with Biomass Smoke Compared with Tobacco Smoke” for BMC Pulmonary Medicine. We appreciate the valuable and detailed comments provided by the reviewers. We have provided the point-by-point responses to the
items below. Please do not hesitate to contact us if you have additional suggestions on the paper. Thank you.

Reviewer 1

1. The title: “Risk of Acute Exacerbations in Chronic Obstructive Pulmonary Disease Associated with Biomass Smoke”

As a suggestion the title maybe would include the term “compared with tobacco smoking”.

Response:

As we agree with the referee, the title has been modified as follows: “Risk of Acute Exacerbations in Chronic Obstructive Pulmonary Disease Associated with Biomass Smoke Compared with Tobacco Smoke” [Page 1 Line 1-2]

2. In introduction section, although the information content in the introduction is clear and enough to delimit the context of the manuscript; it is recommendable that authors propose a hypothesis to justify the analysis performed.

Response: We have added our hypothesis at the end of the paragraph: “We hypothesized that patients with COPD associated with biomass smoke would have a lower risk of exacerbations than those with COPD associated with tobacco smoke as the rate of FEV1 decline is slower in patients whose COPD was associated with biomass smoke than in those whose COPD was associated with tobacco smoke [Reference #14: Ramirez-Venegas A, et al. Am J Respir Crit Care Med. 2014;190:996-1002.]” [Page 5-6 Line 87-91]

3. In Materials and methods section, the methods used are consistent with the study presented, however it is not clear the exclusion criteria used to stabled the four groups, but mainly characteristic of the Less Tobacco-Less Biomass group (n=107), about the origin of the COPD; although actually is it not really a good reference (maybe control group), because have history of exposure to tobacco and biomass as is establishes in table 2. In any case authors included this group, and therefore authors must explain widely why use this group whose patients have history of exposure to biomass exposure and tobacco smoking, in place of use a group without history of
exposition to tobacco or biomass smoke; and also must define what is the cause of the COPD in this group.

Response: We have excluded patients with structural lung diseases because major exclusion criteria of the KOLD and KOCOSS cohorts are patients with respiratory diseases other than obstructive lung disease (e.g., previous pulmonary resection, tuberculosis-destroyed lung, and bronchiectasis). [Page 6 Line 99-101]


4. In results section, newly the Less Tobacco-Less Biomass group (n=107), seems result controversial, because include 32 former smokers and 5 current smokers, with an index of tobacco smoke in pack-years of 1.7 ± 2.9; and additionally a history of biomass smoke exposure of 8.9 ± 7.9 years. In this way, if this is the reference group, their subjects should not have a history of either tobacco or biomass smoke at any time in their lives, and if their COPD were from a source other than biomass smoke or tobacco smoke, it would have to be explained; maybe it was COPD by genetic origin, but it is not indicated. Therefore within the context of the results of this study, the Less-tobacco less-biomass group should include perhaps only subjects who are never exposed to tobacco or biomass smoke, but with COPD.

The questions here is: What are the exclusion criteria to establish each group? Authors must explain it widely in the method section.

Response: We have performed sensitivity analysis with new four groups as the referee suggested (never-exposed to tobacco or biomass smoke vs. exposed to biomass smoke only vs. exposed to tobacco smoke only vs. exposed to both biomass and tobacco smoke). Such analysis showed that patients with COPD associated with biomass smoke and those with COPD associated with tobacco smoke have a similar risk of exacerbations. Please see Tables below.
5. It is not clear why include in the four study groups subjects with history of biomass smoke exposure and also with tobacco smoking history; maybe the groups must be more pure about the population included; because there are several variables that seems difficult the statistical analysis; this is maybe include in the Less Tobacco-Less Biomass (n = 107) only subjects non exposed to tobacco or biomass smoke; Less Tobacco-More Biomass (n = 40) include only subjects exposed to biomass smoke; in the group More Tobacco-Less Biomass (n = 631), considerate only smokers; and in the group More Tobacco-More Biomass (n = 255) include subjects exposed to biomass and tobacco smoke. Also the four groups included former or current smokers; which affect the purity and homogeneity in the study groups.

The question is here, as a suggestion, whether it is possible, depending the study population:

What difference should be in the analysis if only were included only the subjects never-smoker and never-exposed to biomass smoke in the group Less Tobacco-Less Biomass; subjects never-smoker but exposed to biomass smoke in the Less Tobacco-More Biomass; smokers never-exposed to biomass smoke in the group More Tobacco-Less Biomass, and; smokers and exposed to biomass smoke in the group Tobacco-More Biomass?

Response: We have performed sensitivity analysis as the referee suggested.

22 patients who were never exposed to tobacco or biomass smoke vs.

79 patients exposed to biomass smoke only vs.

322 patients exposed to tobacco smoke only vs.

610 patients exposed to both biomass and tobacco smoke

Table S2- Adjusted Incidence Rates of Moderate or Severe Exacerbations by Exposure Groups (see Additional file 1: Table S2)

<table>
<thead>
<tr>
<th>Exposure Group</th>
<th>Adjusted incidence rate* (95% CI)</th>
<th>Adjusted incidence rate ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke only</td>
<td>0.73 (0.59–0.86)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Never-exposed to tobacco or biomass smoke</td>
<td>0.16 (0.01–0.31)</td>
<td>0.22 (0.09–0.56)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Biomass smoke only  0.60 (0.34–0.86)  0.83 (0.51–1.33)  0.437
Biomass and tobacco smoke  0.67 (0.58–0.76)  0.92 (0.74–1.51)  0.477

*Adjusted for age, sex, body mass index, St. George’s Respiratory Questionnaire for COPD (SGRQ-C) total score (<25 vs. ≥25), exacerbation history during the previous year (yes vs. no), and post-bronchodilator forced expiratory volume in 1 s (FEV1)% predicted.

We found no difference in the rates of exacerbations between COPD associated with biomass smoke and that associated with tobacco smoke.

We also applied a propensity score-matched analysis. Forty patients exposed to biomass smoke only were matched with 40 patients exposed to tobacco smoke only. The incidence rates of exacerbations were not significantly different between the groups.

Table S3- Incidence Rates of Moderate or Severe Exacerbations in the Propensity Score-Matched Cohort (see Additional file 1: Table S3)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted incidence rate</th>
<th>Adjusted incidence rate ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1*</td>
<td>Tobacco smoke only</td>
<td>0.50 (0.28–0.72)</td>
<td>1</td>
</tr>
<tr>
<td>Biomass smoke only</td>
<td>0.52 (0.28–0.76)</td>
<td>1.05 (0.55–1.98)</td>
<td>0.890</td>
</tr>
<tr>
<td>Model 2†</td>
<td>Tobacco smoke only</td>
<td>0.48 (0.27–0.69)</td>
<td>1</td>
</tr>
<tr>
<td>Biomass smoke only</td>
<td>0.54 (0.28–0.79)</td>
<td>1.13 (0.59–2.16)</td>
<td>0.721</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>Tobacco smoke only</td>
<td>0.44 (0.24–0.65)</td>
<td>1</td>
</tr>
<tr>
<td>Biomass smoke only</td>
<td>0.57 (0.28–0.86)</td>
<td>1.29 (0.63–2.62)</td>
<td>0.489</td>
</tr>
</tbody>
</table>

*Model 1: unadjusted.
†Model 2: adjusted for sex.
‡Model 3: adjusted for sex, and medication possession ratios of long-acting muscarinic antagonists, long-acting β-agonists, and inhaled corticosteroids during the follow-up period as continuous variables.

We have added this sensitivity analysis at the Methods [Page 9 Line 162-164], and Result section [Page 10 Line 198-206] with supplement Tables (see Additional file 1: Table S2 & S3).

6. It is not well establish why the four study include history of exposure to biomass smoke in years: Less Tobacco-Less Biomass 8.9 ± 7.9; Less Tobacco-More Biomass 35.5 ± 8.3; More Tobacco-Less Biomass 5.9 ± 7.5, and; More Tobacco-More Biomass 37.9 ± 11.2 (<0.001).

Author must explain widely why perform the grouping in this way?, especially because this fact seems difficult the statistical analysis

Response: With all due respect to the reviewer, we believe that we have explained it above.

6. It is not c clear why separate the age limit of 60 years when the standard deviation of the age is near to 10 %. Authors must explain why the limit was established, which seems not be statistically necessary, especially in the group Less Tobacco-More Biomass (n = 40).

Response: We agree with the referee that an age cut-off at 60 years is arbitrary.

7. In the four study groups subjects with history of biomass smoke exposure and also with tobacco smoking history; maybe the groups must be more pure about the population included; because there are several variables that seems difficult the statistical analysis; this is maybe include in the Less Tobacco-Less Biomass (n = 107) only subjects non exposed to tobacco or biomass smoke; Less Tobacco-More Biomass (n = 40) include only subjects exposed to biomass smoke; in the group More Tobacco-Less Biomass (n = 631), considerate only smokers; and in the group More Tobacco-More Biomass (n = 255) include subjects exposed to biomass and tobacco smoke.
Response: With all due respect to the reviewer, we believe that we have performed suggested analysis and presented it above.

8. As a suggestion; authors must discuss their results taking in consideration the two different phenotypes of COPD; by biomass smoke exposure damaging preferment airway than lung parenchyma, and COPD by tobacco smoking affecting mainly lung parenchyma than airways; also that the biomass smoke exposure women, and that women are more susceptible to develop damage to men to tobacco smoking and biomass smoke exposure.

Response: We have described phenotypic differences between COPD associated with either biomass or tobacco smoke exposure in the Introduction section [Page 5 Line 77-80]. We have concluded that clinical and radiological differences between COPD associated with biomass and tobacco smoke may not lead to significant differences in clinical outcomes [Page 12 Line 247-250].

On the other hand, the following sentences have been added in the Discussion section: “However, although controversies still arise, women can be more susceptible of the effects of tobacco and biomass smoke then men, leading to more severe disease for the equivalent quantity of smoke [Reference #1: GOLD 2017 & #35: Foreman MG, et al. Am J Respir Crit Care Med. 2011;184:414-20.]” [Page 14 Line 289-291]

9. Given the differences between parameters such as age, Post-bronchodilator FVC% and FEV1/FVC%, BMI, blood eosinophils, the authors should discuss which are the possible population, genetic, epigenetic, biochemical and physiological causes related to the different conditions in the quality and duration of exposures to tobacco smoke and biomass, which factors are responsible for the presence of COPD, and the fact of the absence in the frequency of exacerbations between groups.

Response: We agree with the referee. However, to mitigate the bias, we applied a propensity score-matched analysis with available covariates including age, sex, BMI, CAT, mMRC, SQRG, exacerbation during the previous year, blood eosinophil, post-bronchodilator FEV1, post-bronchodilator FVC, bronchodilator response, and use of LAMA or LABA or ICS at enrollment.

10. In Table 2 t is not indicated between what of the groups are the statistical P<
Response: P values in Table 2 were calculated from ANOVA, χ2 tests or Fisher’s exact tests, which tested if there were any differences between groups, as described in the Methods section. It is not usual to indicate six P values in each row of Table 2.

Reviewer 2

1. In order to investigate the association between the risk of exacerbations and biomass smoke the inclusion of age 40 in the definition of COPD is problematic as COPD seems to be most prevalent in women under the age of 40 in LMIC (van Gemert, e.a. Lancet Global health 2015;3:e44). Moreover, the distinction between the two most important subgroups of this paper (Less Tobacco-More Biomass and More Tobacco-Less Biomass) is largely determined on the cut-off value of 60 years of age, resulting in a flawed discrimination between the two groups. This is confirmed by Table 2 where age is hardly different between both groups (69.9 vs 67.5 years) while sex is very different (percentage male 35.0 vs 97.8). COPD associated with biomass smoke is not a disease of older men, certainly not in comparison with COPD associated with smoking cigarettes (Boudewijns e.a. J Glob Health 2018;8(2):020306). This a major limitation of the study and should me mentioned in the Discussion and Abstract.

Response: We agree with the referee that COPD associated with biomass smoke is not a disease of older men. In the rural district of Uganda, prevalence of COPD was highest in people aged 30–39 years. However, Uganda is a low-income country with an average life expectancy of 52 years (48 years for men, 57 years for women) as the authors stated [van Gemert F, et al. Lancet Glob Health. 2015;3:e44-51.].

The Republic of Korea is the world's twelfth biggest economy in 2017 (2017 GDP: 1.531 trillion USD) with an average life expectancy of 82.7 years (79.7 years for men, 85.7 years for women). Coal briquettes had been used as the major source of fuel for cooking and heating since the 1950s; however, they had been replaced by gas and liquid fuels from the early 1990s, and biomass fuel use is now negligible (at least in participants of our cohorts).

As we partially agree with the referee, we have added the following sentence as a limitation: “Although we included participants aged 40 years or older, COPD associated with biomass smoke could be prevalent in younger adults [Reference #36: van Gemert F, et al. Lancet Glob Health. 2015;3:e44-51.]. [Page 14 Line 295-296]

We agree with the referee that sex selection bias is a limitation of our study. We discussed it extensively in the Discussion section. To mitigate the bias, we applied a propensity score-
matched analysis with available covariates including age and sex. This approach resulted in the findings consistent with the overall results on COPD exacerbation rates. Please see below.

“Sex selection bias is a commonly encountered issue in COPD research associated with biomass smoke [Reference #11: Zhao D, et al. Respirology. 2018;23:198-2050]. The present study also has the limitation as patients with COPD associated with biomass smoke were predominantly women. To mitigate the bias, we applied a propensity score-matched analysis with available covariates including sex. This approach resulted in the findings consistent with the overall results on COPD exacerbation rates. In addition, no interaction was observed between sex and tobacco and biomass smoke both before and after matching. However, although controversies still arise, women can be more susceptible of the effects of tobacco and biomass smoke than men, leading to more severe disease for the equivalent quantity of smoke [Reference #1: GOLD 2017 & #35: Foreman MG, et al. Am J Respir Crit Care Med. 2011;184:414-20].” [Page 14 Line 283-291]

As we agree with the referee, we have improved the Results section of the Abstract as followed: “Results: Among 1033 patients with COPD, 107 were included in Less Tobacco-Less Biomass (mean age: 67 years, men: 67%), 40 in Less Tobacco-More Biomass (mean age: 70 years, men: 35%), 631 in More Tobacco-Less Biomass (mean age: 68 years, men: 98%), and 255 in More Tobacco-More Biomass (mean age: 69 years, men: 97%). The incidence rates of exacerbations were not significantly different between Less Tobacco-More Biomass and More Tobacco-Less Biomass (adjusted incidence rate ratio, 1.03; 95% confidence interval, 0.56–1.89; P = 0.921). No interaction between sex and tobacco and biomass smoke was observed. When propensity score matching with available covariates including age and sex was applied, a similar result was observed.” [Page 3 Line 50-58]

2. Background:

1) Reference 8 and 9 are from 2006 and 2008. Please use more recent references.

Response: We have substituted the former reference with the updated one, and rephrased the former sentence as followed: “Approximately 25% of premature deaths from COPD in low- and middle-income countries are due to exposure to biomass smoke exposure [Reference #8: World Energy Outlook 2017].” [Page 5 Line 72-73]

2) 'Patients with COPD caused by biomass smoke..'. Please change 'caused by' into 'associated with' or 'most likely caused by'.
Response: We have substituted 'caused by' with 'associated with' in the Abstract, Background, Discussion sections of the revised manuscript (Highlighted).

3. Methods definition of exposure groups

1) Exposure to biomass smoke is defined by 'have you ever burned firewood for cooking or heating by yourself for over a year in your lifetime?'. However, it is also possible that the responder is not the primary cook, but still have been exposed to the biomass smoke. Please mention this as a limitation.

Response: We have added the following sentences as a limitation in the Discussion section: “Third, questions assessing biomass exposure were focused on cooking or heating. However, it is possible that a responder was not a cook, but still had been exposed to biomass smoke.” [Page 13 Line 275-277]

2) It is unclear why you use 1031 cohort participations instead of 1033. 3) It is unclear why non-COPD patients were included in the regression analysis

Response: We applied multiple linear regression in 1031 participants who were not currently exposed to tobacco and biomass smoke including 55 non-COPD patients to find equivalents of exposure to tobacco and biomass smoke before the main analysis. We found that the standardized regression coefficient of $B.4$ ($\beta$) and that of $B.5^*$ ($\beta^*$) were most similar when $m$ was 10 and $n$ was 25 ($\beta = -0.13$ and $\beta^* = -0.14$) (Table 1). Therefore, the tobacco group (More Tobacco) was defined as one with $\geq 10$ pack-years of tobacco smoke, and the biomass group (More Biomass) was defined as one with $\geq 25$ exposure years to biomass smoke. There should be non-COPD patients to predict the diagnosis of COPD in the multiple linear regression model. The same principles apply to predicting post-bronchodilator FEV1/FVC (%). To include non-COPD patients, we performed multiple linear regression in the 1031 cohort participants including non-COPD in a cross-sectional design.

The reason why the number of patients with COPD is different (976 in the cohort for regression, 1033 in the cohort for main analysis) is that the cohort for regression excluded current smokers, but included participants who were followed up for less than 6 months (a cross-sectional design), and the cohort for main analysis included current smokers, but excluded participants who were followed up for less than 6 months. The reason why we excluded current smokers in the cohort for regression is that participants were no longer exposed to biomass fuel for cooking or heating.
in the Republic of Korea. Thus, we should exclude participants who were being exposed to tobacco smoke to find equivalents of exposure to tobacco and biomass smoke.

4. Results:

'After propensity score matching, each of the 16 subjects ..'. It is not clear what these 16 subject refer to.

Response: We used 1:3 matching for 16 patients in the Less Tobacco-More Biomass group and 1:1 matching for other six patients in the Less Tobacco-More Biomass group. We have rephrased the former sentences as followed: “After propensity score matching, each of 16 subjects in the Less Tobacco-More Biomass group was matched with three controls in the More Tobacco-Less Biomass group, whereas each of six subjects in the Less Tobacco-More Biomass group was matched with a control in the More Tobacco-Less Biomass group.” [Page 10 Line 190-193]

5. Discussion:

1) 'We found that patients with COPD exposed to …'. Repetition of the previous sentences; please delete this sentence.

Response: As we agree with the referee, we have deleted the sentence.

2) The limitations of the use of the estimates of 25 years and 10 years are not described very clearly. Please explain it more extensively.

Response: With all due respect to the reviewer, we believe that we have described the limitations of the use of the estimates of 25 years and 10 pack-years in the Discussion section. Please see below.

“However, there are several limitations in these estimates. First, we thought that a multiple linear regression model predicting values of the dependent variable, not post-bronchodilator FEV1/FVC (%) but diagnosis of COPD, would be ideal for determining comparable cut-off values of exposures. While there were only 5% subjects without COPD in the KOLD and KOCOSS cohorts, other prospective cohorts utilizing the same questionnaire on a history of
exposure to biomass smoke were not available in Korea. Second, our regression model using the 
spirometric value as a dependent variable is still limited by the small number of subjects without 
COPD. Third, questions assessing biomass exposure were focused on cooking or heating. 
However, it is possible that a responder was not a cook, but still had been exposed to biomass 
smoke. Fourth, the exposure duration to biomass smoke was defined as the simple sum of 
exposure years to firewood and coal briquettes without weights although the risk of development 
of COPD was greater for wood burners than for coal users. Fifth, exposure to tobacco and/or 
biomass smoke under the cut-off values may cause COPD. Sixth, exposure data on other risk 
factors for COPD, such as indoor/outdoor air pollution and occupational dusts, were lacking in 
our study.” [Page 13-14 Line 268-282]

6. Table 3:

1) Why did you choose to use the 'more tobacco-less biomass' as a reference group?

Response: We want evaluate the outcomes of COPD associated with biomass smoke compared 
with those of COPD associated with tobacco smoke. Comparing its outcomes with those of 
COPD without obvious risk factors is not our objective.

2) The finding that 'more tobacco-more biomass' has a lower adjusted incidence rate (although 
the rate ratio was not statistically significant) is remarkable. Do you have any idea why this is 
lower than expected?

Response: As you mentioned, it is not statistically significant. The incidence rates of 0.72 and 
0.67 are almost the same.