Author’s response to reviews

Title: CHRONIC AIRFLOW OBSTRUCTION IN TANZANIA - A CROSS-SECTIONAL STUDY

Authors:

Thomas Zoller (thomas.zoller@charite.de)
Elirehema Mfinanga (emfinanga@ihi.or.tz)
Trespohy Zumba (tresphoryz@yahoo.com)
Peter Asilia (pasilia@ihi.or.tz)
Edwin Mutabazi (edmutabazi@gmail.com)
David Wimmersberger (davidwimmersberger@hotmail.com)
Florian Kurth (florian.kurth@charite.de)
Francis Mhimbira (fmhimbira@ihi.or.tz)
Frederick Haraka (fharaka@ihi.or.tz)
Klaus Reither (klaus.reither@swisstph.ch)

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Author’s response to reviews:

Dear Dr Flouris,

We are grateful to the reviewers for their comments and their valuable contribution to improving the manuscript.

Below, we provide a point-to-point response to the comments and made changes to the manuscript accordingly.

We hope that the manuscript is now acceptable for publication in BMC Pulmonary Medicine and look forward to hear from you in due course.

Kind regards,

Klaus Reither
Editor Comments:

BMC Pulmonary Medicine operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Helena Backman (Reviewer 1): Review of the manuscript titled: "CHRONIC PULMONARY OBSTRUCTION IN TANZANIA - A CROSS-SECTIONAL STUDY" with Manuscript ID: PULM-D-17-00450.

I find this study interesting and important since data on the prevalence of chronic airway obstruction (CAO) in the African countries is scarce. It is important to recognize that the estimated prevalence is not a population prevalence since it is based on a sample of visitors and patients at a health care facility, and this is also emphasized by the authors, but the results are interesting nevertheless, especially since the population prevalence in Tanzania is unknown. However, there are several major weaknesses that I believe should be addressed before publication.

Major concerns:

*I believe an important analysis is lacking. I would have expected a logistic regression analysis of risk factors for CAO where e.g. age, sex, smoking habits were adjusted for in order to estimate the risk for CAO for subjects who used different methods for e.g. cooking.

Response: in principle, we fully agree to this point and we considered to perform this kind of analysis initially. This study however recruited 50% less patients with CAO than expected from the sample size calculation. We believe that for an analysis with 24 and 30 out of 598 subjects meeting the definition of CAO, respectively, performing a univariate analysis only in this dataset is appropriate, and a multivariate analysis would not add more information and certainty to interpretation of data from this study on pilot-study level.

*In my opinion, it is not unexpected that e.g. FEV1 decrease by the increase in symptom severity since both are strongly dependent on age. Thus, I think the appropriate method is to analyse FEV1 as % of predicted instead for FEV1 per se. In that way FEV1 is adjusted for age, height and sex and those factors are less likely to explain the associations.

Response: we agree with the reviewer and provided an analysis of FEV1/PRED values in table 4 instead.

Minor concerns:
The terminology regarding CAO should preferably be consistent, as for now there are several different terms used, i.e. chronic pulmonary obstruction (in the title and in the methods section on page 4), chronic airflow obstruction (e.g. in the abstract and in the discussion section on page 8) and chronic airway obstruction (in the discussion section on page 7).

Response: we amended the manuscript accordingly and use the term airflow obstruction throughout.

Also, in the background section in the beginning of page 3, I would prefer that the correct name is used for COPD. As for now it is stated "chronic obstructive lung disease" before the abbreviation COPD whereas the correct name is "chronic obstructive pulmonary disease".

Response: we amended the manuscript accordingly and use the term chronic obstructive pulmonary disease where applicable.

Was no consideration taken to the FEV1/FVC ratio when evaluating restriction in the sample? I would have preferred that the ratio of FEV1/FVC should have been higher than the 5th percentile of predicted in combination with FVC lower than the 5th percentile of predicted, and not only FVC lower than the 5th percentile of predicted. This is more in line with previously published definitions of restrictive spirometric pattern.

Response: this comment is correct. The FEV1/FVC ratio should have been included in the definition of restriction. We amended the definition accordingly and re-calculated the values in table 4 and Fig. 1 according to the new underlying study population now including more subjects.

"Positive bronchodilator response according to the ATS/ERS criteria" is mentioned in the Result section but was not defined under methods.

Response: the definition according to ATS/ERS criteria was used and added to the methods section.

Decimal points are sometimes lacking for some results, e.g. in tables 2 and 3 and for the median age on page 5.

Response: corrected in tables 2 and 3. We entered age only in full numbers without decimals in the dataset, therefore the median is given in numbers without decimals.

The column headings in Table 4 are not logical as "n" for e.g. "current or former smokers" is 147 and "% of n" is 29.3. I suggest that the lower case n in the third column of Table 4 is relabelled as upper case N instead.

Response: corrected.
Jens Bräunlich (Reviewer 2): Interesting study that provides data about prevalence of obstructive airway diseases in Tanzania and influence of biomass in development of COPD. The most questionable limitation is the low study population count and only two study centers.

Response: this study does not intend to provide final data on COPD prevalence in Tanzania, but is intended to give first estimates, explore potential risk factors and provide important baseline data for planning and implementing studies on a larger scale. This is discussed at the end of the introduction as well as in the discussion section.

Major comments:

Page 4 Line 91: Why do you not use at this time current GOLD classification

Response: to determine CAO prevalence we actually use both classifications, ATS/ERS as well as GOLD. ATS/ERS definitions are preferred for epidemiological studies whereas the GOLD classification is more widely used in clinical practice due to its simplicity, but with a tendency to over-estimate CAO in older subjects. We also would like to make reference to the ERS statement on the “GOLD controversy” regarding this issue: http://spirxpert.ers-education.org/en/gold-controversy/background/. Furthermore, we discuss the different results of applying both definitions to our study population in the discussion section.

Page 4 methods section: I would prefer to know all inclusion/exclusion data.

Response: the criteria are now given in detail in the methods section.

Page 5 results section: I would prefer to see a flowchart.

Response: we acknowledge the common practice of presenting complex study populations in a flow chart. In the case of this small-scale study, we feel that a flow chart does not give more information than the four relevant figures mentioned in the text in the section “study population”.

Page 5 Line 140 and table 1: Additional demographic data e.g. BMI, kind of business, package years... would be helpful to interpret your data. Are the two centres in a region with mining industry or something else that could influence the results (more urban or more rural, medication with obstructive character, former diagnosis)?

Response: information on the location and setting of the two study sites is given at the beginning of the “methods” section (urban vs. rural, attached to hospitals). The study was not planned nor powered to detect e.g. significant differences among rural vs. urban dwellers, or influence of specific professions. Basic information on occupations among participants is given in table 1.

Page 7 Line 182-187 and table 4: How do you explain this fact? In your study smokers have a better lung function. You should correlate your data with pack years status. If I read your data I would think that biomass fuels for cooking is more dangerous than smoking (exposure time?). Are there informations in the literature about this fact? Are data about both exposures in one
group available? In general proof what do you want to say with this sentence. If you are sure about this fact, please discuss it. Table 4 can be misleading. The p-values are not well allocated.

Response: table 4 was amended according to suggestion of reviewer #1 to include now values of FEV1 vs. predicted instead of absolute FEV1 values. Our intention in this study to provide first estimates and baseline data. The outcomes and correlations mentioned in the comment will need studies on (i) population level and (ii) much larger sample sizes to be investigated sufficiently. This applies in particular to the influence of smoking; only 15% and 13% of participants were active or former smokers. Using FEV1/PRED values, the influence of smoking in this dataset is no longer significant. Larger datasets will be needed to explore influence of smoking in more detail. This is an inherent limitation of a pilot study, and discussed in the respective section.

Page 10 Line 280: Were really all participants able to sign?

Response: in case study subjects were not able to sign for him/herself, the procedure of involving an impartial witness as stipulated in ICH-GCP section 4.8.9. was followed. The respective section in the text now reads: “…gave informed consent either in writing or by an impartial witness”

Was this study registered?

Response: the study was not registered.

Are there parallels or differences to other countries in prevalence?

Response: this is discussed extensively in the 3rd and 4th paragraph of the discussion section.

Minor comments:

Page 7 Line 178-180: This sentence is not clearly enough.

Response: corrected.

Page 7 Line 196: showed showed

Response: corrected.

Page 7 Line 198: Really FEV1/VC ratio?

Response: corrected to read FEV1/FVC.

List of abbreviation: add FEV1, Tiffeneau, GOLD, ATS/ ERS, FVC, JMP, BOLD

Response: we added FEV1, GOLD, ATS/ ERS, FVC, BOLD to the list. Tiffeneau and JMP are individual names, not abbreviations.