Author’s response to reviews

Title: Restrictive spirometric pattern and true pulmonary restriction in a general population sample aged 50 - 64 years

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Author’s response to reviews:

Dear Editor!

We sincerely appreciate this opportunity to revise our paper PULM-D-19-00625 “Restrictive spirometric pattern and true pulmonary restriction in a general population aged 50 - 64 years” following the constructive comments from the reviewers. In response to the reviewers’ comments we have accordingly conducted additional analyses, addressed all enquiries and revised the manuscript accordingly. Especially, we have addressed the suggestion to use SVC by making additional analyses. We address below the referee’s comments, in a point-by-point manner. The changes in the manuscript are marked with bold text. However, changes in Tables and the added Figure are not marked with bold.

Reviewer 1
1. We agree on that comment, and we have added Figure 1 plotting the sensitivity and specificity of RSPLLN using increasing percentiles of FVC. This is described in Methods, page 7 and the Results, page 8.
2. All spirometry was performed in accordance with ATS/ERS guidelines (Miller MR, ERJ 2005;26:948-968). This has been further stressed in “Methods” and the relevant reference has been added to the manuscript.
3. We have made additional analyses using SVC instead of FVC. This is described in the Introduction, Methods, Results and in the new table, Table 3. These results were very interesting, and we thank the reviewer for this suggestion. These results are further mentioned in the Discussion.
4. We do not have any registration of ethnicity. The population is mixed, and the reference values are from the same mixed source population. We have not further discussed that.

Specific comments.
1. We have added N2-washout to the abstract
2. We have added severe obesity and neuromuscular weakness in the Introduction.
3. We have not further commented upon why some studies claim that RSP is more common in low- and middle-income countries. But if the Editor, so wish, we can expand the discussion about this theme.

Reviewer 2
1. We agree that we have included subjects 50-64 yrs of age, but our study design is based on a general populations sample from this narrow age interval, 50 to 64 yrs. This has now been added in the Discussion. We agree that this limits the external validity of our results and this is discussed accordingly at page 10 in the Discussion.
2. Our results indicate that regarding the validity of RSP in relation to true pulmonary restriction, there was no obvious difference between pre- and post-bronchodilator results.
3. We agree, there are vast number of studies showing the age difference regarding chronic airflow limitation depending on whether CAL was defined according to GOLD or LLN. The difference is, however, not so obvious in the age interval 50 to 64. We have shown that in previous studies on this material as, for example Torén et al, IJCOPD 2016. However, in this manuscript, we consider it to be beyond the scope of this analysis to discuss that.
4. We agree that it would have been beneficial to have a population with a larger age interval. The SCAPIS study was designed to include subjects aged 50-64 yrs. This age range was chosen as the main aim of SCAPIS is to identify risk markers that allow prediction for which individuals are at risk of developing cardiovascular disease. We acknowledge that the narrow age range is a serious limitation of the external validity and this is discussed at page 10 in the Discussion.
5. Unfortunately we do not have the information asked for by the Reviewer.
6. We have added data about diabetes mellitus and myocardial infarction in the description of the population, Table 1.
7. We thank the reviewer for the suggestion. We have now have reported the prevalence of dyspnea and asthma in the different groups in Table 1. Unfortunately, the power of study is too low as we generally have less than five cases in each subgroup.

Reviewer 3
1. The reviewer asks for analysis of thresholds of FVC. We agree on that comment, and we have added Figure 1 plotting the sensitivity and specificity of RSPLLN using increasing percentiles of FVC. This is described in Methods, page 7 and the Results, page 8.
2. Yes, we agree, that in a clinical population with higher prevalence of restriction, RSP may be more valid. We have added a few lines about this in the discussion.
3. We have added more information about the quality controls regarding pressure, volume and flow for the body plethysmograph.
4. We have made additional analyses using SVC instead of FVC. This is described in the Introduction, Methods, Results and in the new table, Table 3. These results were very interesting, and we also thank also Reviewer 3 for this suggestion. These results are further mentioned in the Discussion.

Additional changes
In addition to the points raised by the reviewers we have made following changes in the manuscript;
1. We have changed RSPGOLD to RSP0.7.
2. We have added “sample” to the title.
3. We have made a number of corrections of the language.
4. We have also added a Table in a supplement.
Yours sincerely,

Kjell Torén
Senior professor