Reviewer’s report

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

Version: 0 Date: 18 Dec 2019

Reviewer: Kazuhiro Yamaguchi

Reviewer's report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Comments to the authors

General comment

The authors tried to examine the "true" lung restriction that is defined as the reduction in TLC measured by the body plethysmography from the surrogate indicator estimated on the basis of the simple spirometric data of FVC and FEV1/FVC before and after bronchodilator inhalation, which has been defined as the "restrictive spirometric pattern (RSP)" in the field of lung function testing. The subjects examined are invited from the general population registered in the Swedish CArdioPulmonary bioImage Study (SCAPIS Pilot), comprising 983 adults with very narrow age range between 50 and 64. This narrow age range of the recruited subjects are indeed problematic when separating the true restriction from the RSP. The lower-limit-of-normal (LLN) and upper-limit-of-normal (ULN) of TLC measured by the body plethysmography are practically height-dependent but age-independent. However, the LLNs and ULNs of body-plethysmography-decided FRC and RV are generally age- and height-dependent. Furthermore, the LLNs (and ULNs) of FEV1, FVC, and FEV1/FVC depend on both age and height, suggesting the subjects with RSP selected by applying the fixed cut-off value of FEV1/FVC (i.e., 70%) and FVC (i.e., 80%) differ substantially from those by the age-dependent LLN when the subject's age is young or old. However, since the age-dependent variable LLN passes through the fixed cut-off point at 50-60 years, the middle-aged subjects selected for RSP based on the fixed cut-off value is not largely different from those selected based on the age-dependent LLN. These facts certainly indicate that the fixed cut-off value and age-dependent LLN (or ULN) have almost the same meaning as to the selection of subjects with RSP in case of the target being middle-aged persons. Therefore, it is meaningless to simultaneously use the fixed cut-off value and the age-dependent LLN for judging the abnormality of a certain lung function parameter in middle-aged persons. The comparison between the results obtained from the fixed cut-off value and those from the LLN makes sense when the subjects with a wide range of age are included for the analysis. The authors should recognize such a decisive drawback in their study (see below).

Major comments

1) The reviewer supposes that the subjects recruited for the present study do not meet the criterion for "general population" randomly selected. This is because the age range is restricted from 50 to 64 years.
This is the intentional selection and difficult to say that the subjects enrolled for the present analysis propagate the nature of general population in Sweden. Therefore, the reviewer disagrees with the authors' opinion that "the present study is the first one in a general population sample validating RSP in relation to true pulmonary restriction" (p. 9).

2) The finding of no difference between pre- and post-bronchodilator results on the relationship between true restriction and RSP is potentially interesting, indicating that the inhalation of bronchodilators is not needed for adequately diagnosing the airflow limitation. However, these are highly inconsistent with the recommendation by GOLD and other authorized guidelines for COPD. The authors should discuss in detail why the inhalation of bronchodilators had no effect on the extent of airflow limitation in their study.

3) The authors found that there is no difference in RSP prevalence estimated from the fixed cut-off value and that from age-dependent LLN. As indicated in the general comment, the reviewer is quite convinced that this is artificially induced by the selection vias of the subjects. As demonstrated by several investigators (cf. Mannino et al., Thorax 2007;62:237; Cerveri et al., Thorax 2008;63:1040, and so forth), the fixed cut-off value of 70% for FEV1/FVC adopted by GOLD for identifying the airflow limitation overestimates the prevalence of subjects with morbid airway obstruction (i.e., COPD) in a group of elderly persons but underestimates it in a group of young persons. This is because the LLN value of FEV1/FVC decreases with advancing age and the age-dependent LLN line crosses the horizontal line of 70% at a middle age around 50 to 60 years. Since the age distribution of the subjects used in the present study is 50~64 years, the dissociation between the LLN and 70% line is expected to be small, indicating that the prevalence of subjects with or without airflow limitation matches accidentally between the condition where 70% is used, and that where LLN is used, for defining the airflow limitation. The same holds true qualitatively for FEV1 and FVC (fixed cut-off value of 80% or LLN), as well.

4) There are a vast number of the epidemiological studies regarding the RSP (cf. Godfrey et al., Chest 2016;149:238). The age distribution of the subjects in most of the epidemiological studies are wider than that in the present study. The reviewer would like to ask the authors about the essential rationale why they should invite the subjects with age between 50 and 64 years. The Swedish SCAPIS Pilot may be a large-scaled cohort study. Therefore, the authors could select the subjects with a wide range of age, for example, from 20 to 90 years. If the subjects with a wider age distribution is chosen for the RSP analysis, the comparison of the estimation from LLN and that from fixed limit such as 70% for FEV1/FVC will make sense but it is meaningless when the subjects with a narrow age range, particularly with middle age range, are selected.

5) The discordance between true restriction and RSP was found to be significantly associated with overweight and increased RV. The latter has not been clearly reported so far. Hence, this may be a new point found in the present study. Then, the reviewer would like to ask the authors about the causes eliciting the reduced RV in their subjects. The RV reduction is generally caused by the excessive fat accumulation in the thoracic and/or abdominal cavities (morbid obesity), diffuse pleural adhesion, thoracic deformations such as kyphoscoliosis, or interstitial lung fibrosis. The reviewer requires the author to provide the data (including CT images) for surely explaining the pathophysiological backgrounds of the subjects with reduced RV.

6) The RSP has been considered to be associated with metabolic syndrome (i.e., systemic inflammation), including diabetes mellitus, cardiovascular diseases, including pulmonary hypertension and cardiac failure, and so forth. The reviewer requires the authors to analyze the prevalence of RSP
subjects who have the above diseases.

7) The RSP has been identified to have the association with significant respiratory symptoms with a relatively high mortality. The authors should analyze the qualitative and quantitative differences in respiratory symptoms between the subjects with true restriction and those with RSP.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?
5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.