

## Peer Review File

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### Reviewer A

**Comment 1:** *The authors have evaluated whether individuals with non-obstructive spirometry-defined small airway dysfunction have impaired exercise capacity as compared to both subjects without COPD and subjects with GOLD I COPD. They show that individuals with SAD have impaired exercise capacity that may be associated with ventilatory inefficiency regardless of smoking status. Overall, the study is well-conducted and I've only one major comment and two minor comments that are the following.*

**Response 1:** We thank the reviewer for positive comments related to our manuscript. We have carefully edited the manuscript during the revision. Detailed responses are listed below.

**Changes in text:** Without modification.

**Comment 2:** *SAD definition: ideally the authors should have used GLI predicted values based on ethnicity. This is important because it allows to better (more confidently) define SAD as a decrease in FEF25-75% < 5th percentile for instance. The use of Caucasian predicted values is disputable.*

**Response 2:** We agree with the reviewer that it would be better to group according to

the GLI 2012 reference equations for South East Asian populations. A number of parameters have been used to assess small airway function, including MMEF, FEF50, FEF75, FEV<sub>3</sub>/FVC, FEV<sub>3</sub>/FEV<sub>6</sub>. Among these, at least two of MMEF, FEF50, and FEF75 having below 65% of the predicted values is the most widely used method in clinical practice and research [Lancet Respir Med. 2020:1081-1093]. However, it is a pity that there is no FEF50 in the GLI 2012 reference equations. For these reasons, we decided to maintain the original analysis in the main text.

To verify whether the results of the primary analyses were robust, we incorporate an analysis defining SAD as a post-bronchodilator spirometry MMEF<80% of the predicted value based on the GLI equations [Eur Respir J. 2017;49(3):1602055] as a further sensitivity analysis. We get results consistent with the main results of the paper. Results of the new sensitivity analyses are presented in the new Supplementary Table S6 and we refer to this in the main text.

**Changes in text: Line 148-152, Page 8:** Add the sentence in the methods of sensitivity analyses: “Third, subjects were grouped using the Global Lung Initiative 2012 reference equations for South East Asian populations”. **Line 211-212, Page 11:** Add the sentence in the results of sensitivity analyses: “These group differences in the risk of impaired exercise capacity remained present when we change the reference values (Table S6)”. **Supplementary material:** Add new Supplementary Table S6.

**Comment 3:** *Several "trends" are discussed, but when P value is > 0.05 the result is not significant. Nevertheless, trends can be discussed in the Discussion section.*

**Response 3:** Thank you for your valuable suggestion, and we have modified the description in the article to make it more accurate and clearer.

**Changes in text: Line 191-193, Page 10:** Change the sentence "...there was a trend towards higher  $\dot{V}_E/\dot{V}CO_{2AT}$  ( $\beta=1.1$ ; 95% CI  $-0.1$  to  $2.3$ ;  $p=0.07$ ) in the SAD group (Table 4)" to "...there was a trend towards higher  $\dot{V}_E/\dot{V}CO_{2AT}$  in the SAD group that nearly reached statistical significance ( $\beta=1.1$ ; 95% CI  $-0.1$  to  $2.3$ ;  $p=0.072$ , table 4)".

**Line 249-250, Page 13:** Change the sentence "We found that  $\dot{V}_E/\dot{V}CO_{2AT}$  tended to be higher in patients with SAD..." to "We found that  $\dot{V}_E/\dot{V}CO_{2AT}$  marginally higher in patients with SAD...". **Line 254-255, Page 13:** Change the sentence "Further research

is required to confirm this speculation" to "As the difference of  $\dot{V}_E/\dot{V}CO_{2AT}$  between SAD and controls did not reach statistical significance ( $p = 0.072$ ), further research is required to confirm this speculation". **Line 257-258, Page 13:** Change the sentence

" $\dot{V}_E/\dot{V}CO_{2AT}$  tended to increase in both smoking and nonsmoking patients with SAD..." to " $\dot{V}_E/\dot{V}CO_{2AT}$  increase slightly in both smoking and nonsmoking patients with SAD...".

**Comment 4:** *Table 1: the never-smoking groups are ~20% (GOLD I) and ~40% (SAD) that is quite high. Table S1 shows that women are more frequent in the non-smoker groups, which could be discussed.*

**Response 4:** We agree with the review that the percentage of non-smokers in our SAD and GOLD I groups is higher than that reported in most studies. Nevertheless, apart from smoking, other risk factors for SAD and COPD such as passive smoking, biomass

use, outdoor air pollution are also prevalent in China (especially in the female population) [Thorax 2017;72:788–795; Thorax 2007;62:889–897; Lancet Respir Med. 2020:1081-1093]. The percentage of non-smokers in groups and the percentage of women among non-smokers in this community-based study was similar to other multicentric studies conducted in China [Lancet. 2018;391(10131):1706-1717], which suggests that it is a representative sample. We have addressed this in the Discussion section as follows: Our study extends these findings to never-smokers and found that patients with SAD who had never smoked also had impaired exercise capacity. This finding has implications for better recognition of chronic respiratory diseases in developing countries where outdoor air pollution and exposure to tobacco smoke are increasingly prevalent (**Line 255-259, Page 14**).

**Changes in text:** Without modification.

## **Reviewer B**

**Comment 1:** *The authors conducted an observational retrospective analysis of exercise capacity and ventilatory efficiency in patients with SAD, GOLD I compared to those without SAD or airflow obstruction. The study sheds the light on another angle of the early signs of COPD. It was previously reported (DOI: 10.2147/COPD.S261732, DOI: 10.1136/bmjresp-2022-001385) that small airways impairment as measured by MMEF is an early marker of COPD, however the burden of it on other factors such as exercise capacity and ventilatory efficiency needed to be evaluated. Despite the authors great*

*efforts, the manuscript needs some amendments to help readers evaluate and understand the importance of the reported findings.*

**Response 1:** We really appreciate the comments. We have carefully edited the manuscript during the revision. Detailed responses are listed below.

**Changes in text:** Without modification.

**Comment 2:** *It does not seem that this was a prospective study, as previously collected data was used. This is a retrospective, cross-sectional analysis of previously collected data, therefore it should be labelled as so.*

**Response 2:** For epidemiological perspective, the primary difference between retrospective and prospective studies is study design. Data in the *National Science and Technology Support Plan Program for the 12th and 13th Five-Year Plans* were collected after the study design and follow-up of participants is still ongoing. The time frame for conducting a data analysis or making a conclusion may depend on the amount of data we can collect and the execution of the research. Therefore, we think this is a prospective study. However, our current study is a cross-sectional study based on data from the *National Science and Technology Support Plan Program for the 12th and 13th Five-Year Plans*. To avoid confusion, we do not use “prospective” in the main text.

**Changes in text:** **Line 6, Page 1**: Change “This prospective, multiyear cross-sectional study” to “This community-based, multiyear cross-sectional study”. **Line 69, Page 5**: Change “which were population-based, observational prospective surveys of COPD” to “which were community-based, observational surveys of COPD”.

**Comment 3:** *Bonferroni is a statistical correction method used on top of statistical difference tests such as T-test or Mann-Whitney. Please define how statistical analysis was conducted and how distribution normality was assessed.*

**Response 3:** We are very sorry for causing any confusion. This has been corrected in the revised manuscript.

**Changes in text: Line 130-137, Page 8:** Change the sentences “Demographic and clinical characteristics were compared between groups using analysis of variance for continuous variables and the chi-square test for categorical variables. The Bonferroni method was used to analyze significant differences among multiple groups” to “A Kolmogorov–Smirnov test was used to explore whether the quantitative information accorded with normal distribution. A one-way analysis of variance or Kruskal–Wallis test were used to evaluate differences among control, SAD, and GOLD I groups, adjusted for multiple comparisons using Bonferroni correction method. Chi-squared tests or Fisher’s exact tests were used to compare the difference in categorical variables”. **Table 1, Table 2, Table S1, Table S2, and Table S3**: Change the sentence in the note of table: “...were compared between the groups using analysis of variance for continuous variables and chi-squared tests or Fisher’s exact tests for categorical variables” to “...were compared between the groups using one-way analysis of variance or Kruskal–Wallis test for continuous variables and chi-squared tests or Fisher’s exact tests for categorical variables”.

**Comment 4:** *I do not understand the reason the authors used the 1993 European Community for Steel and Coal reference ranges. The reference ranges are for those from European decent, and not applicable to those of Chinese origin. I believe the GLI reference ranges are most suitable as they contain the reference ranges for people with Chinese origin.*

**Response 4:** We agree with the reviewer that it would be better to group according to the GLI 2012 reference equations for South East Asian populations. A number of parameters have been used to assess small airway function, including MMEF, FEF<sub>50</sub>, FEF<sub>75</sub>, FEV<sub>3</sub>/FVC, FEV<sub>3</sub>/FEV<sub>6</sub>. Among these, at least two of MMEF, FEF<sub>50</sub>, and FEF<sub>75</sub> having below 65% of the predicted values is the most widely used method in clinical practice and research [Lancet Respir Med. 2020:1081-1093]. However, it is a pity that there is no FEF<sub>50</sub> in the GLI 2012 reference equations. For these reasons, we decided to maintain the original analysis in the main text.

To verify whether the results of the primary analyses were robust, we incorporate an analysis defining SAD as a post-bronchodilator spirometry MMEF<80% of the predicted value based on the GLI equations [Eur Respir J. 2017;49(3):1602055] as a further sensitivity analysis. We get results consistent with the main results of the paper. Results of the new sensitivity analyses are presented in the new Supplementary Table S6 and we refer to this in the main text.

**Changes in text:** Line 148-152, Page 8: Add the sentence in the methods of sensitivity analyses: “Third, subjects were grouped using the Global Lung Initiative 2012 reference equations for South East Asian populations”. Line 211-212, Page 11: Add the

sentence in the results of sensitivity analyses: “These group differences in the risk of impaired exercise capacity remained present when we change the reference values (Table S6)”. **Supplementary material:** Add new Supplementary Table S6.

**Comment 5:** *Throughout the paper, decimal places are inconsistent. Please use a consistent methodology of how you report the decimal places, especially p values.*

**Response 5:** We modified the decimal places and thank the reviewer for pointing this out. We have changed p values to 3 decimal places for neatness. Regression coefficients were quoted to a single decimal. Odds ratios and correlation coefficients were quoted to 2 decimal places. For demographic data, spirometry and cardiopulmonary exercise testing measures, we use appropriate decimal places for the accuracy of resolution estimation [Eur Respir J. 2022;60(2):2101821 and Respir Res. 2022;23(1):298].

**Changes in text: Line 183, Page 10:** Change “ $p=0.22$ ” to “ $p=0.215$ ”. **Line 188, Page 10:** Change “ $p=0.07$ ” to “ $p=0.069$ ”. **Table 3:** Change all  $p$  values to 3 decimal places.

**Table 4:** Change all regression coefficients to single decimal place. Change all  $p$  values to 3 decimal places. **Table S4 and S5:** Change all  $p$  values to 3 decimal places.

**Comment 6:** *Line 7, it should be ‘from’ not ‘for’.*

**Response 6:** The sentence has been modified.

**Changes in text: Line 7, Page 1:** Change the sentence “...collected in Guangdong, China for 2012–2019...” to “...collected in Guangdong, China from 2012–2019...”.

**Comment 7:** *Line 15, the sentence is a discussion rather than result. It should be*



*removed.*

**Response 7:** We are very sorry that we didn't write it clearly. As it is one of the highlights of our study that the risk of impaired exercise capacity was still higher in nonobstructive SAD than in controls when never-smokers and ever-smokers were considered separately. Instead of simply delete this sentence, we rewritten it and hope that it is now better understandable.

**Changes in text: Line 15-18, Page 1:** Change the sentence "These findings were robust in never-smokers and ever-smokers" to "Results were consistent within subgroups of smoking status (Ever smokers: SAD vs. controls, aOR = 2.44; 95% CI: 1.08 - 5.51; never smokers: SAD vs. controls, aOR = 2.38, 95% CI: 1.02 – 5.58)".

**Comment 8:** *In table 1, the n/N is confusing, just use n (%).*

**Response 8:** We are very sorry for causing any confusion. The n/N actually is intending to show the missing values. Similar problems have been revised to make the meaning of the expression clearer.

**Changes in text: Table 1 and Table S1:** Change "n/N (%)" to "n (%)". Add a sentence in the note of table: "‡ Numbers of subjects with Symptoms available: Chronic cough =472, Chronic sputum =478, Wheezing =467". **Table 2, Table S2, and Table S3:** Change "n/N (%)" to "n (%)".

**Comment 9:** *Table 3, use univariate instead of 'crude'.*

**Response 9:** Similar problems have been revised in the manuscript.

**Changes in text: Table 3, Table S4, and Table S5:** Change “crude” to “univariate”.

**Comment 10:** *Line 176, the subheading is a discussion phrase.*

**Response 10:** It has been revised in the manuscript.

**Changes in text: Line 184, Page 10:** Change the subheading “Potential reason for impaired exercise capacity in SAD” to “Associations between ventilatory efficiency and exercise capacity in SAD”.