Peer Review File
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Reviewer A

Comment 1: Why had authors included children with only mild to moderate disease? It would be exciting to see a correlation between lung physiology with C-ACT.
Reply: the current study is a secondary analysis of data collected from our previous interventional study and therefore the inclusion criteria is based on the aim of the parent study, which is to examine the effects of two-week bedroom air purifications on the asthma-related outcomes among children with mild or moderate asthma. In the revised manuscript, we have discussed the population representativeness as a study limitation.
Changes in the text: in lines 265-268, we have added "Second, this study only included children with mild or moderate asthma due to the inclusion criteria of the parent study that provided data for the current analysis. Therefore, we cannot evaluate the relationship between C-ACT and lung pathophysiology in children with severe asthma.

Comment 2: The sample size is very small to power the primary outcome.
Reply: As mentioned above and in the original manuscript, the current study is a secondary analysis of data of an interventional study. The sample size was determined to provide sufficient power to detect significant effects of air purification on FeNO. As described in our previous publication, a sample size of 40 individuals would provide 90% power to detect significant FeNO changes at 0.05 levels. We have revised the manuscript to better clarify the nature of this study as a secondary analysis.
Changes in the text: in lines 88-92, we have clarified that "In the present study, we conducted secondary analysis of data collected from a clinical trial in which 43 children with mild or moderate asthma were followed bi-weekly for six weeks for the assessment of C-ACT as well as hospital-based measurements of lung function, airway mechanics and respiratory inflammation. However, only 37 children had complete data on C-ACT score for the current analysis."

Comment 3: The 6-week follow-up is a very short period to assess the mentioned outcome. I think authors should have at least 3-6 months periods of follow-up.
Reply: Again, the current secondary data analysis was constrained by the parent study design. To minimize the potential seasonal influence to the the effects of indoor air purification, the parent study used a cross-over randomized trial design with a 2-week intervention period. Hence the total follow-up period of each child was 6 weeks long, comprised of a 2-week true purification, 2-week sham purification, and a 2-week washout in between the true and sham purification (order randomized). We agree with the reviewer for a longer period of follow up if the study were originally designed for the current analysis.
In this study as a secondary analysis to illustrate the relationship between C-ACT score and lung pathophysiology, the short period is indeed an important limitation. This limitation is acknowledged in the revised manuscript.

Changes in the text: in lines 261-265, we stated “First, we conducted repeated measurements within a relatively short period of six weeks during which no asthma exacerbation events were reported. A longer follow up period may be more desirable to examine the relationship between C-ACT score and lung pathophysiology, considering that clinical events such as asthma exacerbation and an asthma phenotype change may affect the relationship.31-33

Comment 4: At baseline, all have well-controlled asthma (i.e., C-ACT >19) except 3 children, and 30% were not taking any long-term asthma medication. Therefore, it is very obvious such children might develop exacerbation and decrease in C-ACT score and PFT parameters. To obviate this, authors should have included only newly diagnosed cases of asthma.
Reply: Yes, various factors such as medication and air purification, may affect future changes in C-ACT score and pathophysiological parameters. However, the goal of this study is to examine whether real-world variations in C-ACT score, resulting from effects of a combination of exposure, can reflect changes lung pathophysiology. We did not have any subject with newly diagnosed asthma, given one of the inclusion criterions that the child must have at least one episode of asthma exacerbation during the past 12 months.

Comment 5: In C-ACT, the parental questions item response is taken over the last 4 weeks; however, in this study, C-ACT was applied every 2 weeks, which may bias the study.
Reply: we agree with the reviewer’s comment. We have discussed this point as a study limitation in the revised manuscript.
Changes in the text: in lines 268-273, we added “Third, this study followed up each subject for up to six weeks and only capture short-term variations in C-ACT score and lung pathophysiologic indictors. More importantly, although we assessed C-ACT score and measured lung pathophysiology every two weeks, the caregiver questions were designed for four weeks, which may partially explain the poor correlation between caregiver’s score and pathophysiologic indicators.”

Comment 6: The authors mentioned that C-ACT is a subjective measure of asthma control, while GINA mentioned it as a numerical and more objective tool for asthma control assessment.
Reply: we believe that C-ACT is a more objective tool than the qualitative method, while it is in a form of questionnaire and therefore has a subjective nature. Nevertheless, we have removed the discussion on subjective vs. objective in the revised manuscript to avoid any potential confusion.
Changes in the text: we have deleted the description of C-ACT as a subjective measure throughout the manuscript.

Comment 7: The discussion part should be precise and can be shortened.
Reply: we have edited the discussion section thoroughly to increase its conciseness.

Please refer to the revised manuscript for specific changes we have made.

Reviewer B

Comment: The present study reported that longitudinal c-ACT decrement up to 2 or more in one particular subject was associated with lung respiratory mechanism and FeNO. Although the differences of FEV1, FVC and R5 were statistically significant, the differences were so small after considering the variability of the test and minimal clinical significant differences of these parameters. It might be overstated the significance especially in the situation that there were not data of subjects with the stable or improved c-ACT.

Reply: we agree and appreciate the reviewer's constructive comments. Indeed, our observation is based on children with mild or moderate asthma and with good asthma control. In the revised manuscript, we have toned down our conclusions and clarify it applies to children with mild or moderate asthma only. In the limitation sections, we have also emphasized that our findings cannot be readily extrapolated to severe asthma or patients with poor asthma control.

Changes in the text:

Abstract: we have revised the conclusion into "In children with mild or moderate asthma, longitudinal C-ACT score changes could reflect acute changes in large airway resistance and lung function. Measures of small airway physiology would provide valuable complementary information for asthma control. Asthma phenotype may affect whether C-ACT score could reflect respiratory inflammation."

Lines 265-268: we have added "Second, this study only included children with mild or moderate asthma due to the inclusion criteria of the parent study that provided data for the current analysis. Therefore, we cannot evaluate the relationship between C-ACT and lung pathophysiology in children with severe asthma."

Line 279-281: we have revised the conclusion as "In this longitudinal study of 37 children with mild or moderate asthma, within-person changes in C-ACT scores were significantly associated with changes in same-day measurements of airway resistance and lung function."