Author's response to reviews

Title: Methacholine Bronchial Provocation Measured by Spirometry versus Wheeze Detection in Preschool Children

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Author's response to reviews: see over

Dear editorial Team,

We thank the reviewers for their helpful comments.

Enclosed please find our answers to both reviewers, hopefully all comments have been addressed properly by providing a point by point response to them and by revising our manuscript accordingly.

All changes are marked in red.

Please note that Daphna Volizni (last author) is the corresponding author to this work.

Thank you for everything

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Reviewer 1

We thank the reviewer for his/hers time and constructive comments.

Enclosed please find our responses to you comments, hoping all issues will be clarified:

1. Is it as useful in a random sample of young children? Many questions remain open as to the usefulness of this test in a random sample of young children and/or how discriminating this test is as a diagnostic tool. It would be also necessary to assess the sensitivity of this test to various severities of disease. See page 13, line 5 from the end.
2. How discriminating is it as a diagnostic test? See above.
3. Does it add any more to asking if they wheeze? Added: "… In this respect we would argue that FEV_1 does make a contribution beyond simply asking the subject if they wheeze." See page 12 line 2 – end of paragraph.

Suggestions:

Abstract: In lines 2 and 7 the acronym MCH is used. It should be MCT for the test as in the body of the paper. Done

Methods, page 5:
It states that consecutive referred children were recruited.
A) Did every suitable child accept, if not how many did not?
Of 62 families asked to participate in the study, seven refused. Added to Subjects, page 5, line 3.
B) Training time was limited to 15 minutes per child – Added at page 6 line 22.

Methods, page 6:
In line 2 it states that the dose was halved if the child coughed or wheezed.
This does un-standardize the test as children would then be receiving a different cumulative dose. –
This may be the case, yet we felt that safety considerations were more important than standardization. – page 6 lines 2-6. In the light of the risk of airway closer as shown by the spirometry during the test, the MCH increment was only half the usual amount when transient wheeze or cough was noted, keeping in mind that the accumulative dose is affected by this manipulation.
In line 12, the unit mgr is used which is not the usual- this is fixed.

In Analysis and Statistics, page 7:
The correlation Co-efficient is used to compare PCW and PC20.
Justification is required as it would be highly likely that the correlation would be significant, but it doesn't tell us anything about the level of agreement, which would be important in the application of the tests. – We have added the Blant and Altman test for level of agreement between the tests – see: Page 7 line 20; Page 10 line 2; Page 12 line 4 and Figure 3

In Results, page 8: There is a Vbe of approximately 3% which is exceptional in this age group with low VC and quite different to all other reports. Please explain.
Vbe ≤5%FVC found in our study is narrower than reported [11], as we have rejected in advance curves with Vbe >5%FVC at the expense of success rate. (Page 11 lines 5)

In Discussion, page 10: They state that MCT was feasible in 65% of our preschool children. As this was a group of referred wheezy children, this statement cannot be made. It was feasible in this group of children.
The sentence was fixed to: We found MCT was feasible in 65% of our wheezy preschool children (discussion line 3)

Page 12: They explain reduced FVC and flows as due to increased negative intrathoracic pressure, but this is a forced expiratory maneuver with positive intrathoracic pressure. The intra-bronchial pressure in asthmatic children could be lower with increased peripheral resistance. The sentence was eliminated. Special thanks for this comment.
They also suggest glottic narrowing but the flow volume curves are not suggestive of upper airway narrowing. Added to the text:
Reduced FVC may also be due to increased glottic narrowing due to MCH irritation [26,27], but the flow volume curve was not suggestive of upper airway obstruction (trimmed PEFR). Alternatively, the upper airways response to methacholine may contribute to the increase in total respiratory resistance [27]. (Page 12 lines 19)

In the 5th last line, they state that PC20 may result in lower MCH concentrations. It would be better to say ' may be achieved with inhalation of lower MCH concentrations.' Fixed accordingly. (Page 13 lines 8)

Page 13: The last lines should also state that it is necessary to assess rigor as a test in diagnosis and management of asthma in this age group.
Added: page 13 lines 19… Yet, many questions remain open as to the usefulness of this test in a random sample of young children and/or how discriminating this test is as a diagnostic tool. It would also be necessary to assess the sensitivity of this test to various severities of disease.

Table 1b: GINA criteria - Column eliminated.

Table 2: Rhonchi are no longer considered a standardized term. Column eliminated.

Reviewer's report:

It is a pity, however, that they did not report FEV 0.75 or FEV 0.5, as this is probably more relevant and might have given improved feasibility.
We have added FEV0.5 to the paper. See page 11 line 16 and on.
In that respect we found that PC_{20}-$FEV_{0.5}$ occurred at a mean concentration value of 1.29-±1.47 mg/ml, meaning that the responsiveness of the airways in the preschool age may be similar to that of infants, despite differences in the measurement techniques. It is important to note that PC_{20}-$FEV_{0.5}$ occurred at a significant mean lower concentration than PC_{20}-FEV_1 (1.96-±1.83 mg/ml; $p<0.01$), however, standardization is needed to accept the PC_{20}-$FEV_{0.5}$ value for the determination of hyper-reactive airways.

Major compulsory revision

1. It is not clear whether or not PC values were log- transformed before statistical analysis. They should be if means are used and this should be stated, in which case ˜means should become geometric means.
Indeed we have used log- transformed values.
This is now stated in the paper. (Medians did not significantly differ from the mean).
See page: 7 line 6.

Minor essential revisions

1. The intra-subject reproducibility, as calculated, is usually termed the coefficient of variation. It would be helpful if it were called this on page 8. Also, as this is a methodological paper, it would be useful to have **ranges** of the variation found not just mean values. Ranges have been added in relevant places.

2. Similarly, (last para page 9) the range in falls of SaO2 etc would be informative.
Ranges have been added in relevant places.

3. Readers are often confused by correlation. In this study PC wheeze and PC20 show an extremely tight correlation but they are not the same. Either a **Bland and Altman plot should** be used or comment explaining the possibility of being mislead by high correlations.
Special thanks for this comment. A **Bland and Altman plot** is added in Figure 3.
Page 7 line 20; Page 10 line 2; Page 12 line 4

4. **Abstract (line 2**) unfeasible is a clumsy way of saying not possible.
Changed.

5. ***Abstract* para 3**. The **insertion of the %** of 36/55 would be helpful – Added.

6. **On page 8** it is stated that all children previously had shown a bronchodilator response. How if they were spirometry-naive at the time of study inclusion?
Page 8 line 10: The 36 children participating in both tests had a previous response to bronchodilators as judged by clinical observation.

Discretionary (optional) revision

1. Since the authors confirm the lack of sensitivity of PC wheeze, with some almost alarming associated falls in FEV1 and SaO2, perhaps a stronger warning about its use would be in order.

Page 13 line 12: using PC20-FEV1 (or PC20-FEV0.5) can avoid inhalation of higher concentrations of MCH used to achieve wheeze, leading to alarmingly diminished flows found at PCW and a significant shortening of test time relative to PCW.