Author's response to reviews

Title: Exhaled nitric oxide is related to atopy, but not asthma in adolescents with bronchiolitis in infancy

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Version: 4 Date: 30 July 2013

Author's response to reviews: see over
Dear Editor,

Thank you for the opportunity to submit a new revision of this manuscript.

We have considered all comments and proposals from the two reviewers, and made alterations accordingly.

We have used a red font to indicate the revised portions of our manuscript.

The work has not been published before and is not being considered for publication elsewhere.

All authors have significantly contributed to the work and have approved the final manuscript.

There are no conflicts of interest for any of the authors.

Sincerely,

Ingvild Bruun Mikalsen
REVIEWER # 1
CHRISTOPHE MARGUET

The manuscript and the results have been improved and done more readable, and specified most of the comments.

Thank you.

In the discussion, the first paragraph evoked the low FeNO levels that the authors found whatever the subgroups. These levels were roughly less than 20ppb. This should be specified at this place of the discussion.

We agree and have specified this in the first paragraph of the discussion.
Major Compulsory Revisions

1. Abstract Conclusion last sentence: insufficient data to make such an inference.

   We agree, and have rewritten and modified the conclusions.

2. Paragraph “Study Design”: This study has the design of a case-control study rather than a cohort study. The cases should be children that have been hospitalized during infancy due to bronchiolitis having the characteristics described in the first paragraph and controls should then be children that have not been hospitalized due to bronchiolitis. Therefore, the unselected age-matched control group should by definition exclude those children that have been hospitalized. If this is the case please refer it appropriately. Moreover, all inferences should be based on this fact and all results should be cautiously interpreted.

   Thank you for this comment which has been thoroughly discussed in our group and also with our statistician, who also confirms the statements below.

   Our conclusion is that the study cannot be considered as a case-control study. Porta’s Dictionary of Epidemiology defines a case-control study as an observational epidemiological study of persons with the disease (or another outcome variable of interest) and a suitable control group of persons without the disease (comparison group, reference group).

   This is a longitudinal follow-up study of a group of subjects identified during their first year of life due to “exposure” to hospitalization for bronchiolitis. To date, this group has been followed for 11 years, and various outcomes have been reported in a series of articles.
In this particular paper, FeNO levels in the post-bronchiolitis group were compared to FeNO levels in a comparable control group, “unexposed” to hospitalization for bronchiolitis in their first year of life. Thus, FeNO was the outcome variable, while hospitalization for bronchiolitis was a potential explanatory variable. We therefore argue that this study is not designed as a case-control study.

Moreover, the bronchiolitis group was included during hospitalization for bronchiolitis in the first year of life, while the control group was included at 11 years of age. Thus, those exposed to hospitalization for bronchiolitis were followed prospectively, while the control group was examined once, as in a cross-sectional design. Based on this, we have characterised this study as a prospective follow-up of children hospitalized for bronchiolitis in their first year of life with a historical control cohort.

However, in the revised version we have clarified the definition of the control group, by adding a comment that children in the control group were not hospitalized for bronchiolitis.

3. Section Results 3rd paragraph: The sentence “there was no other ... and control group, separately” is confusing with regards the compared groups. Does it refer to the comparison among all the four subgroups per study group (post-bronchiolitis and control) or between the two groups (post-bronchiolitis and control) as a whole? In any case it will be better to clearly mention the groups and subgroups to be compared in the methods section.

We acknowledge this comment, and agree that this may be confusing. The comparisons were done among all the four subgroups in each of the main groups (post-bronchiolitis and control groups). We have rewritten in the result section to clarify (page 9).

I also believe that when referring to the subgroups in both the manuscript and tables, using the term “atopic non-asthmatics” instead of just “atopic” will be more informative.

We agree and have changed this term.
4. Paragraph FENO – Table 3: In this table it is stated that “no significant interaction effects were observed between…” This finding could be just explained by lack of power (this model has 8 groups) and not necessarily by lack of true statistical significance. This should be discussed and highlighted appropriately.

We appreciate this important comment. We agree that the lack of interactions between these groups could be explained by lack of power. We have underlined this further under strengths and limitations.

In addition, we should not forget that this is a case-control study. The regression beta-coefficients under the Table 3 subtitle “Sub-groups by atopy and asthma status” correspond to the healthy, atopic non-asthmatic, non-atopic asthmatic and atopic asthmatic individuals independently of the group they belong (either from post-bronchiolitis or control group) since the interactions are non-significant. That means that cases and controls have been pooled in each subgroup and compared accordingly. This approach contradicts the design (case control) and the aims of the study listed in the last paragraph of the introduction. It could be commented though as an extra secondary outcome but without dedicating to many paragraphs and tables in the results and discussion. Both comments (lack of power and interpretation of non-significant interaction effects) apply to all analyses performed including the regression model and results in Table 5.

As discussed above under item 2, we do not consider this a case-control study. In the overall ANOVA analyses (Table 3) and the regression analyses (Table 5) the group exposed and the group unexposed to hospitalization for bronchiolitis in their first year of life were analysed together, in order to assess if FeNO differed between the groups, to answer the primary aim of the study.

However, in the ANOVA analyses (Table 3), the model included both the interaction term (subgroups x control/post-bronchiolitis variable) as well as the main effects of each variable. As the interaction-term (subgroups x the control/post-bronchiolitis variable) was not significant, this term was removed from the overall ANOVA model.

This does not mean that the post-bronchiolitis and control subjects have been pooled in in each subgroup and compared accordingly.
However, we have rewritten to present and discuss these results more accurately in this revised version of this paper. In the revised version we have focused less on the results regarding interactions between the subgroups, and have omitted some paragraphs in the result and discussion sections.

5. Section Discussion: There is a recent publication [Konstantinou et al. JACI 2013; 131(1):87-93] suggesting that there is an episodic increase of FENO during viral wheezing independently of the atopic status. This increase subsides after the episodes are gone, rendering wheezers comparable to normal individuals outside episodes. In addition, there seems to be an association between FENO and lung function when both parameters are assessed longitudinally and in an individualized manner. Please comment and quote it in the relevant paragraphs in the discussion.

   Thank you for reminding us of this important publication. We have discussed this paper in the revised Discussion section, page 11.

6. RSV negative subjects are not enough to perform powerful statistical analyses and the authors should be very cautious in their inferences and subsequent assumptions.

   We agree, and have added a comment about this under strengths and limitations.

Minor Essential Revisions
1. Abstract methods: rephrase “a skin prick test” to “skin prick tests”

   We have changed this.

2. The subtitle “follow up” is redundant.

   We have omitted this subtitle.

3. Paragraph Skin Prick Test: After “…to common local … food allergens add in parenthesis the allergens listed and the relative reference.
We have changed accordingly.

4. Paragraph “Regression analyses of potential explanatory factors…”: Change the order between 2nd and 3rd paragraph.

   As the results in paragraph number 2 are based on the results from paragraph number 1, we find it to inappropriate to change the order between these paragraphs.

5. There is no need to separate the discussion with subtitles in different subsections.

   As several issues are discussed in this paper, we suggest keeping the subtitles in order to make this paper more clear and readable. However, we agree to omit them if requested by the editor.