Reviewers report

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

Version: 3 Date: 14 June 2013

Reviewer: George Konstantinou

Reviewers report:

Major Compulsory Revisions

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

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.

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. 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.

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.

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.

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.

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.

Minor Essential Revisions
1. Abstract methods: rephrase “a skin prick test” to “skin prick tests”
2. The subtitle “follow up” is redundant.
3. Paragraph Skin Prick Test: After “…to common local … food allergens add in parenthesis the allergens listed and the relative reference.
4. Paragraph “Regression analyses of potential explanatory factors…”: Change the order between 2nd and 3rd paragraph.
5. There is no need to separate the discussion with subtitles in different subsections.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.