Author's response to reviews

Title: Early eczema and the risk of childhood asthma: a prospective, population-based study

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Author's response to reviews: see over
Re-submission of manuscript: "Early eczema and the risk of childhood asthma; a prospective, population-based study"

Dear Editor,

We thank you for the opportunity to resubmit our manuscript. We have made a point-by-point answer to both of the referees. Hopefully, the manuscript has improved.

Yours sincerely,

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Reviewer: Marie-Soleil MSM Masse

Major Compulsory Revisions:

1) Is there a statistically significant difference between eczematous vs. non-eczematous patients according to the percentage of subjects with positive skin tests?

**RESPONSE:** The sample-size of those tested is quite small, as can be viewed by the width of the estimated CIs. When going through our manuscript, we found that the percentage given on sensitized children in the children subsample were wrong. We apologise for this. The correct numbers can now be found in the manuscript on page 11, second sentence. There was no statistically significant difference between eczematous vs. non-eczematous children. A p-value (p=0.7) has been added in the text.

2) Although the authors refer us to an appropriate previous work, the actual skin tests used in the study should be named in the manuscript. At least, it should be specified that both respiratory and food allergens were tested.

**RESPONSE:** Information regarding actual skin test used is included in the manuscript, under the heading “Methods”, sub-heading “The Random Subsample”, page 6 first para.

3) Authors should have mentioned, in their discussion, that a major limitation of the study is that only 12 different allergens have been tested. Moreover, important allergens known to cause eczema were not included in the panel (e.g. wheat, soybean)

**RESPONSE:** Since there are limitations to the number of prick test applied to the small forearms of 2-years old children, we had to be strict in our selection of allergens tested. The decision on which allergens to choose were taken after discussions with some of the top experts on eczema and allergy in Norway. Based on clinical experience, and results from a similar study on a general population in Sweden (were 2% of children with eczema at age 2 years had positive SPT to wheat and 1% of the same children had positive SPT to soy, Ref Bøhme M et al. Acta Derm Venereol 2001;81:193-197), these two allergens were left out of the study. We have already included in our discussion that one of the limitations of the study is the possibility that children are sensitzed towards allergens not tested for (page 13, first sentence). We have added wheat and soybean as examples of this.

4) Concerning the 95% CIs given, there at a lot of them who do not seem to be possible. For instance, 95% CIs for age at delivery seem awkwardly narrow (mean age 29.8, 95% CI 29.6-30.0 vs 28.9, 95% CI 28.7-29.1). Moreover, some 95% CIs are used inappropriately in the descriptive statistics (for eg the Table 1 and the characteristics of the patients).

**RESPONSE:** The reason for the narrow 95 % CI for mother’s age at delivery is that this is a large population of women in reproductive age. 95 % CI for the mean can be estimated by using the formula:
We know that the standard deviation for mean age at birth of delivery is 4.50 for those with follow-up data, and 4.79 for those without follow-up data. 95% CI for mean age at delivery for those with follow-up data can therefore be estimated: $29.8 \pm 1.96 \times \frac{4.5}{\sqrt{2192}}$, $29.8 \pm 0.19$. This gives the 95% CI for the mean as stated in the article. The same analysis can be performed for those without follow-up data. We have changed the descriptive information on mean age, and now give the $+/\text{- SD}$ instead of the 95% CI. We hope this is more informative (page 8, under the heading “Results”, line 8).

Further, we have used 95% CI in our descriptive statistics (table 1), as this is widely used and recommended in epidemiological studies. We have estimated all of them a second time, without finding any mistakes. The estimates are quite precise, due to the large sample size.

Minor Essential Revisions

1) There are a lot of spelling mistakes in your manuscript: I would recommend that someone fluent in English revise your manuscript. Here are some examples:

   a) In the abstract: Results: Association between ever eczema 2 years and current asthma 6 years was aOR=1.80 = this sentence bears no sense.
   b) “debut”
   c) “where”
   d) “etics”

RESPONSE: We have had the manuscript edited by someone fluent in English. To the best of our knowledge, spelling mistakes are now corrected. You will also find that there are several re-writings. Hopefully this has made the article better.

Discretionary Revisions

5) Another limitation is the use of Immulite 2000 method for dosing allergen-specific IgEs. The standard used in manuscripts for dosing IgEs is, nowadays, ImmunoCAP – Phadia

RESPONSE: We are aware of this. However, at the time when this study was performed, we had to use the test that was offered us at our university hospital. This was Immulite 2000.

6) Finally, some results are displayed in the methods section of the manuscript (in the statistics section of the methods part).

RESPONSE: The information given in statistics section: “Some 143 children (66% boys) who reported ever having doctor diagnosed asthma at age 2 years were excluded from the follow-up analyses” has been changed to: “Children with a history of doctor-diagnosed asthma at age 2 years were excluded from the follow-up analyses.”
Reviewer: Caimmi Silvia Maria Elena

Major compulsory revisions:

1) This manuscript considers a large cohort of patients with eczema at age 2 years, with the aim of studying the risk of developing asthma and allergy coexisting at the age of 6 years. The authors’ interest is to test the hypothesis of an atopic march in the general population, however, the considered population is not general, but a group of children already affected by eczema.

   RESPONSE: This is not a group of children already affected by eczema. The design is that of a cohort study, where exposure (history of eczema) is registered at baseline (2 years), and the outcome (current asthma) is reported at 6 years of age. The cohort consists of 4,780 2-years old children considered representative of the general population. The prevalence of eczema at baseline 2 years is 16.7% (as reported in table 2). As expected in cohort designs, we compared those exposed (exposure here being “history of eczema at age 2 years”) with those unexposed (unexposed here being those “without a history of eczema at 2 years”) regarding outcome (“current asthma at age 6 years”). In doing so, we found an increased odds ratio for asthma at 6 years of age among exposed compared with unexposed.

2) The structure of the article makes interpretation difficult: the results and discussion are reported before methods and statistics.

   RESPONSE: We are sorry about the inconvenience this may have caused. We have now formatted the paper according to recommendations from BMC Pediatrics.

3) All the study relies on the answers of parents of detailed questionnaires on the child’s health. Thus it is difficult to make a diagnosis of asthma or wheezing, which may be due to viral infections, very frequent in the age group considered and which are not associated with the atopic march.

   RESPONSE: Yes, this is a questionnaire-based epidemiologic study, where parents answer detailed questionnaires on their child’s health. We have validated the eczema diagnosis against the United Kingdom Working Party’s diagnostic criteria. Several of the questions have also been reliability tested, and doctor diagnosed asthma at age 2 years was found to have excellent agreement (kappa 0.88). We are well aware that both asthma and wheezing among small children may be due to viral infections, and not necessarily associated with the atopic march. This is why we have removed all cases of doctor-diagnosed asthma at 2 years of age from our analyses. We have also repeated the analyses after having removed both asthma and wheeze at 2 years of age from the analyses, without substantial different results (last two sentences under the heading Methods, sub-heading Statistics). As for current asthma at age 6 years, we have chosen a rather stringent definition, with positive report of both doctor diagnosed asthma AND use of asthma medication. To emphasize the high validity of mother-reported use of anti-asthmatics, we have added the following sentence: ”In addition; mother-reported use of anti-asthmatics during the previous year among 7-year-old children is showed to be highly valid” (Page 12 line 7). Ref. Furu et al.
For these reasons the conclusions are not supported by reliable datas or objective datas.

RESPONSE: We disagree in this statement as explained in our responses.

After reading the manuscript I have not learned anything new.

RESPONSE: There are only a few publications studying the atopic march in an unselected general population. That is why this paper, according to our point of view, adds new insight to the hypothesis of an atopic march.