Author’s response to reviews

Title: Risk factors for eczema in infants born in Cuba: a population-based cross-sectional study

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Author’s response to reviews: see over
Dear Dr Henderson,

Re: Risk factors for eczema in infants born in Cuba: a population-based cross-sectional study

Thank you for giving us the opportunity to respond to the reviewers’ comments on this manuscript. We have modified the manuscript and hope that this is satisfactory. In addition, my Cuban colleagues noted that the presentation of the Spanish names in the acknowledgements was not correct and have rectified this.

Best wishes,

Dr Andrew Fogarty
Nottingham, UK. 10.2.2014

Reviewer 1

Comment 1. Methods: More information is required regarding definition of exposures. This will affect the interpretation of the results. For example, insect sting allergy, which was associated with eczema, seems unexpectedly common (52% according to Table 2). How was insect sting allergy defined? Is it likely that there has been misclassification here? Also, where cut-offs were used for continuous variables, please explain why these were chosen. For example breastfeeding was categorised at less than or more than 4 months – why was this cut-off chosen?

Authors’ response
We agree that the prevalence of insect sting allergy is high. The question that was used to collect these data has now been added to the methods so that this is explicit (below).

Data on insect sting allergy were collected using the question “Has your baby been diagnosed with insect sting allergy in the first year of life”

The aim of the analysis was to assess epidemiological risk factors for allergic disease and not compliance with best practice or WHO guidelines. We thus pragmatically chose 4 months as it was a cut off for breastfeeding that provided (almost) a balanced split (45% and 55%) between the two categories created, thus allowing more power to detect differences in the outcomes of interest. The alternative would have been to divide into above and below the median value which would have provided a perfect 50%/50% split but would have been less intuitive for the reader.

Comment 2. Methods: Please provide some information on how the sample size for the study was arrived at and provide an indication of statistical power to detect risk factors for eczema.

Authors’ response
The original grant proposal was powered to detect the risk of paracetamol exposure on the risk of eczema. We have added the power calculation to the manuscript (below).

Sample size
We aimed to collect data on 2000 children. In the first year of life eczema is a better measure of allergic disease than wheeze and we have used this for the primary power calculation. We anticipated that we will have over 95% power (Epi-info, StatCalc) to detect an increase of the odds ratio of eczema of 1.9 for those who receive any paracetamol in the first year of life compared to those who do not receive paracetamol conservatively assuming a baseline prevalence of eczema of 20% and that 10% of the children in the cohort will receive paracetamol at some point in the first year of life.
Comment 3. Methods: It would be important to test for linearity for continuous variables such as weight and maternal age and eczema, as the association between these factors and eczema may not be linear.

Authors’ response
We did this but it was not explicit in the text. We have added the following text to the statistical analysis section of the methods.

**Associations of the outcome with exposures that were continuous variables were checked for linearity using likelihood ratio tests.**

Comment 4. Results: Study participation was very high (96%), which is a key strength of the study. What proportion of infants had complete data for all the variables listed in Tables 1 and 2?

Authors’ response
As the data were collected by interviewer administered questionnaire that was directed to the parents/guardian, we had complete data for most infants. Where data were missing it is indicated by the totals in Table 1 and Table 2. The only exposure where we had a considerable amount of missing data was for the parasite measurements which required a separate faeces sample. We have added this to the Table 2 as it was not explicit previously.

Comment 5. Results: Please include P values for Tables 2 and 3. These would provide an indication of the strength of the evidence for an association for each factor and could be used to better assess the likelihood that an observed association was due to chance, which is particularly important given the large number of individual comparisons made in Table 2.

Authors’ response
We would prefer to present the results using the confidence intervals as this gives an assessment of the size of the estimates of the associations of interest as opposed to the p value, which gives a simple measure of the probability of the association being observed. The reasons for this are outlined in a paper called ‘Confidence intervals rather than P values: estimation rather than hypothesis testing’ by Gardner and Altman (Brit Med Journal 1986;292:746-750). In addition, the p values for our exploratory analysis are almost impossible to interpret due to the multiple hypotheses being tested. This is considered in the discussion (below).

Finally, we have tested a number of exposures and hence are unable to exclude the possibility that some of the associations we observed are the consequence of chance.

Comment 6. Results: Was information collected on number of siblings? If so, the relationship between number of siblings and eczema should be explored rather than simply the presence or absence of siblings. Previous studies have often reported that number of siblings is important in risk of allergic disease.

Authors’ response
There was no association between the number of siblings and the risk of eczema. We have omitted this detailed information from the text as we have already reported that there is no association between siblings and risk of eczema in Table 1.

Comment 7. Discussion: There are some additional potential limitations to the study design that should be discussed. Is it possible that recall bias may have affected the results? For example, is it possible that likelihood of recognising and reporting eczema differed by maternal age? There is also the possibility that the study was unable to adequately control for confounding in some of the analyses because potential confounding variables were unmeasured or measured inaccurately. This may be particularly important when examining the association between paracetamol exposure and eczema. Although the association persisted after adjustment for reported symptoms of wheeze, respiratory infections may also have occurred in the absence of wheeze and episodes of wheeze during the first year of life might not be accurately recalled by parents when the child is
one year of age.

Authors’ response
We have added this important limitation to the discussion.

We are unable to exclude the possibility of recall bias and residual confounding influencing our data and the associations reported.

Comment 9. Methods – Study population: the ethics sentence appears to be missing a comma between “National Institute of Hygiene, Epidemiology and Microbiology” and “the local Havana Scientific Committee”
Authors’ response
Thank you – we have added this.

Comment 10. Discussion paragraph 1 and conclusion: “an younger mother” should be “a younger mother”
Authors’ response
Thank you – we have changed this in the two bits of highlighted text.

Comment 11. Discussion paragraph 4, 1st sentence should read “no comparable studies”
Authors’ response
Thank you – we have added this.

Comment 12. Discussion, paragraph 7, 1st sentence: this does not make sense as currently written and needs to be revised.
Authors’ response
Thank you – we have changed this to two sentences resulting in improved grammar and meaning.

To our knowledge, the inverse association between maternal age and risk of eczema has not been reported previously [20,21,22,23]. Maternal age is closely related to birth order as older mothers have more children, and this is considered to be a risk factor for allergic disease, with individuals with more elder siblings having less hayfever and eczema [24].

Comment 13. Conclusion: Second sentence should read “The delivery of high quality observational...
Authors’ response
Thank you – we have changed this.

Comment 14
Discretionary Revisions. It would be useful if some information could be provided on how representative the study population is of all infants in Havana. Is there any information available on (for example) median maternal age for all mothers in Havana, or what proportion of infants are born by caesarean section?
Authors’ response
We are sorry that we are unable to provide these data. As our sample is population-based with an excellent response rate, this will provide good estimates for the populations from which our participants were sampled.

Reviewer 2
The reviewer provided an annotated file so we have transcribed his comments so allow ease of evaluating our response.

Comment X11. Is insect sting allergy so frequent at that age?
Authors’ response
We have checked the frequency again and this is correct. Please also see the definition of insect sting allergy outlined above in response to the comments of Reviewer 1.

Comment X12. How determined, visual, culture.
Authors’ response
We have clarified this in the text.

and self-reported mould in the home (OR 1.23; 95% CI: 1.07-1.41).

Comment X13. Both diseases are quite different.
Authors’ response
We have removed the mention to scabies.

Comment X14. I do not understand this sentence
Authors’ response
We have edited the sentence to remove any potential ambiguity.

Data on the height and weight at both the time of birth and the interview were also collected.

Comment X15.
Authors’ response
We have added the word “we”.

Comment X16.
Authors’ response
We have modified the text as presented below.

The use of the ISAAC questionnaire definition of eczema allows comparison of our data with other similar studies [11], but it is possible that this practical epidemiological approach to defining the outcome measure may have a degree of imprecision as other causes of itchy rashes in addition of eczema may be included in the outcome measure.

Comment X17. I do not understand an ecological risk factor.
Authors’ response
We have removed the words ‘ecological and individual’ as they are not essential and obviously lead to some confusion.

Editorial requests

Please also address the following editorial requests in your revised manuscript.

1. Abstract
In line with our Instruction for Authors (http://www.biomedcentral.com/bmcdermatol/authors/instructions/researcharticle#formatting-abstract) we ask that the Abstract section contains a "Methods" subsection.
Authors’ response
We have done this. I am sorry that we missed it first time.

2. Authors Contributions
Please ensure there are no inconsistencies in this section. At present it is stated, "The data were collected by the 10 Cuban authors (SF, RW, EF, GG, II, LM, DO, HH)...") This should read "8".
Authors’ response
We have done this.
3. Copy-edit
Please be thorough in checking your manuscript for any typographical or language errors.
Authors’ response
We have done this.

4. Consent
Please clarify whether "written informed" consent was obtained from the parents of the children in this study.
Authors’ response
We have done this.

5. Formatting
As stated in our Instructions for Authors, we ask that any tables be placed after the references.
Authors’ response
We have done this.