Author's response to reviews

Title: Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study

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Author's response to reviews: see over
Title: Increased prevalence of asthma and other allergic conditions in Colombia (changed now to “Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study”).

Date for version No. 2: 08-Nov-2011

Dear Editors:

Please find attached our revised manuscript entitled “Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study” for consideration of publication in BMC Pulmonary Medicine.

We would like to thank all three reviewers for their comments and critique. The revised manuscript addresses all the reviewers’ comments. We think that the revised manuscript is now much improved in clarity due to their observations. Below please find our point by point answers to the observations.

No part of this manuscript is under consideration in any other journal. All authors have reviewed the manuscript and approve of its content. As described in the manuscript, all authors have contributed significantly to the manuscript. No author discloses any conflict of interest that relates to this work.

We thank you in advance for your consideration of this revised manuscript and for the length of time provided to us to revise it.

Respectfully,

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Reviewer Prof. Grize:

MAJOR COMPULSORY REVISIONS.

Title:

- Please adjust the title to your results or present comparison of results of the present study with those from the previous (ref 16).

Reply: In this new manuscript version, we have now decided to abstain from a formal comparison of the two surveys over time due to the challenges involved in a strict epidemiological/methodological comparison (with the limitations discussed later in this reply). The new title is “Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study”

Abstract:

- The objectives given here (apart from the first) are different to those given in the main text. Please re-state your objectives in the abstract and background.

Reply: This was done basically due to space limitations in the abstract. We have harmonized both now.

- In the conclusions, it is said that the symptoms prevalence of the described diseases are higher than a decade ago but it is not indicated which were the prevalence a decade ago. Please complete the results.

Reply: Given the new emphasis of the manuscript on results of the current survey, and much less to a comparison of surveys over time with our previous work, this has now been changed: “In Colombia, symptom prevalence for asthma, AR and AE, as well as levels of atopy, are substantial. Specifically for asthma, symptom severity and absence from work or study due to symptoms are important. These primary care sensitive conditions remain an unmet public health burden in developing countries such as Colombia.”

Methods:
• Please be sure that you show all the relevant questions for the definition of the allergic
disease or disease symptoms.

   Reply: We have decided to add a new table with the relevant questions or definitions used
   (table 1).

• Results for disease severity are given, but how was this determined? Which were the
   questions posed? If the questions were the same as those of one of the ISAAC phases,
   please give the appropriate references, if not, please write them in this section.

   Reply: We have changed the relevant paragraph in the methods section. The definitions
   for severity and for previous medical diagnosis of the three conditions were identical to
   those previously used in other ISAAC studies and can be found at

Results:

• The same methodology should be used for both surveys, weights should be calculated for
   the first survey and then comparisons made. This only if the measurement methods were
   the same (relevant questions to each disease symptoms) in both surveys.

   Reply: We have insufficient information to perform the comparisons suggested by the
   reviewer. While methods were similar in the two surveys (as well as questions posed to
   participants), we lack access to the previous study database to do additional analyses, as
   suggested by the reviewer. Thus, a formal comparison between the two times that
   requires any data re-analysis is not possible. We have then decided to abstain from a
   formal comparison of the two surveys over time in the current manuscript, and rather
   concentrate on the current survey, with limited inferences with the previous survey in the
   “discussion” section, as suggested by the reviewer.

• The reader should have numbers from the previous survey at hand.

   Reply: Because of the above limitation and the focus now on current results, this is now
   not necessary.

• Since allergic conditions are different for different age groups and sexes at different
   stages of their life, an overall prevalence adjusted for the different socio-demographic
   factors should be presented. From the manuscript text it would be assumed that the
   weights would take care only of sample demographic issues.

   Reply: All post-stratification adjustments were weighted by the Colombian 2009 census
   projections for gender, age and city. Specifically for the 5 to 17 year old group, weights
   were combined with the sampling frame of students registered for the academic year
   2009-2010 in Colombia. Prevalence estimates are adjusted by city, age and gender. We
   have made this clearer in the methods section and in the tables now.
Discussion:

- **Was the questionnaire in the current survey similar enough if not identical to the first survey?** In the previous survey, the definition of asthma is based on two questions....this is the same for rhinitis and eczema.

  Reply: We thank the reviewer for taking the time to review our previous published survey as well. The definitions for current and lifetime symptom prevalence of asthma, rhinitis and dermatitis, their severity, and previous medical diagnosis of the three conditions were identical for both surveys and to those previously used in ISAAC studies.

  The two-question “case” definition for asthma was used in the previous study to invite subjects to provide a blood sample to test for atopy. This was the case as well for working definitions on “rhinitis” and “eczema” for data analysis. In the present study, the case-definition changed to make data collection in the field simpler. Noteworthy, there was no control group in the previous survey. We apologize for the lack of clarity.

- **The prevalence in this manuscript are (survey) weighted but not in the results from your reference 16. The comparisons are quite not fair.** Specially that, on atopic eczema, in the first survey it was asked “have you (or your child) had an intermittent itchy rash for at least six months in the past 12 months? Which does not seem to be the case in the present manuscript. Besides, there seems to be quite a difference on the distribution of educational level.

  Reply: The definition on current symptoms of atopic eczema was the same in both surveys; in the actual manuscript we have now made the definition clearer. As mentioned before, we lack access to the previous study database to do additional analyses, as suggested by the reviewer. Thus, we have included in the discussion the following paragraph: “The current study used the same questions as the ISAAC initiative worldwide, and was conducted in the same cities in Colombia as a previous study from the same research group eleven years ago [16]. However, differences in age groups, methods and in data analysis, as well as in allergens used for sIgE, preclude a formal comparison between the two surveys, or with others conducted previously in Colombia and abroad. Thus, contrasts discussed here can only suggest potential tendencies over time.”

- **The classification of atopic subjects based on specific IgE levels is based on tests to different allergens, here also, comparisons are not fair.**

  Reply: This is correct. Please see above.

- **Sentence on “Differences of allergen sensitization between cases and controls could be greater if we had included...” should be part of the study limitations.**

  Reply: This has now been included in the discussion of study limitations: “Differences of allergen sensitization between cases and controls could be greater if we had included...”
more allergens such as Dermatophagoides farinae, Alternaria tenuis, Ascaris lumbricoides, cockroach, grass/tree pollen mix [31], but financial limitations and the population-based design precluded this.”

- If you would like to make the point that in developing countries...please give some numbers from the cited references...
  
Reply: We have now modified the discussion section to reflect this.

Conclusions:

- Please rephrase the first sentence “...this conditions” to “...allergic conditions”.
  
Reply: Done now.

- The conclusion should reflect what is reported in the results....please change discussion or complement results.
  
Reply: Conclusion is changed now as per the points above.

MINOR ESSENTIAL REVISIONS:

- In general: there are a few syntax errors...
  
Reply: Agreed. We have now reviewed the manuscript again.

- In tables: add sample size to the tables...
  
Reply: This has been corrected now for tables 2-6, thanks.

- In the references: check that all references are cited in the format required by the journal...
  
Reply: this has been corrected now, thanks.

- In the results: it is stated that the prevalence of AE symptoms was greater in females, was this statistically significant? Just looking at the numbers in the tables it does not seem so. Please rephrase sentence if necessary.
  
Reply: The difference was statistically significant (Z=3.25; P=0.003). This is to be expected given the large sample size. However, since we do not show any point by point statistical comparisons in the manuscript but confidence intervals, we have decided to modify the sentence to: “...but there was an increased tendency for females...”.

- In the results: Under asthma it is stated that “Similar variations were found for the lifetime...but not by physician diagnosed asthma”, the prevalence are given. Tables 2,3,4
show, approximately, the same variation but not the same prevalence. Please rephrase one or another, or if both, make two different sentences.

Reply: This has been done now: “Variations by city and age group, but not by sex, were also found for the lifetime accumulated prevalence of asthma symptoms; the overall prevalence was 23% (95% CI, 21.1-24.8). The overall prevalence of physician-diagnosed asthma was much lower than symptom-based prevalences (7%; 95% CI, 6.1-8.0).”

- Other revisions, including DISCRETIONARY REVISIONS:

  Reply: These have now been corrected.
Reviewer Prof. De Sario:

MAJOR COMPULSORY REVISIONS.

Study design.

- It’s worth if the authors can add a comparison of socio-demographic characteristics of the study subjects with the source population in the six cities to check for possible selection bias. It could be interesting whether (the authors) provide at least which proportion of resident population the participating subjects are, for each city and age group considered.

Reply: We regret that the section in the “methods” section was not clear on this. In our design, post-stratification weight adjustments were calculated to ensure that city, age, and gender composition in the sample was the same as in the sampling frame and census projections. They are thus similar. We have modified the pertinent paragraph in the “methods” section: “….Post-stratification weight adjustments were calculated to ensure that city, age, and gender composition in the sample was the same as in the sampling frame and census projections. Prevalence estimates are adjusted by city, age and gender....”

While providing information on the proportion of the resident population that participated in the study can be interesting, we feel it may not add significantly to the data already provided.

Study population.

- I advise authors to discuss that respiratory viral infections have an important part to play in the production of wheeze in this age group and asthma diagnosis is difficult.

Reply: This has been done now. The pertinent paragraph in the discussion section reads as: “...The age group where asthma symptoms were most frequent in both surveys was the 1-4 year old group. It is likely that some of these symptoms correspond to wheezing episodes associated with respiratory viral infections early in life [27]; recent evidence, however, also suggest that bronchial obstruction during acute respiratory infection in childhood is clearly associated with subsequent asthma, especially among school-aged children at risk for repeated asthma exacerbations [28], making it relevant to quantify and to include in epidemiological studies.”

- With regards to control selection in the nested case-control study, I ask authors to discuss if the restriction to people without allergic rhinitis and atopic eczema may have reduced the prevalence of exposure in the controls below that in the source population of cases, biasing the results.
Reply: This is a good point. We believe that including subjects with these two conditions may have biased results for atopy above those of the source population sampled (because of their well known association with atopy). But we cannot test this hypothesis either. We have decided to include a sentence in the discussion under limitations that reads: “... our choice of controls to assess differences in atopy (excluding those with allergic rhinitis and atopic eczema) can be questioned; while such exclusions may have biased the prevalence of atopy in the control group below that in the source population of cases, we believe that exclusion of these two conditions provide a better estimate of the prevalence of atopy in the population sampled.”

- **I suggest to motivate why people with mental problems were excluded.**

Reply: people with an altered mental state, dementia, or mentally challenged were excluded because of the difficulty in collecting and assuring validity of information. This has been now included in the methods section.

Data collection.

- **Authors should discuss other allergens of potential interest in the study population.**

Reply: These have been included now in the discussion section, with an additional reference: “…we used only two allergens for diagnosing atopy, therefore it is possible that the effects of cross reacting antibodies were more relevant. Differences of allergen sensitization between cases and controls could be greater if we had included more allergens such as Dermatophagoides farinae, Alternaria tenuis, Ascaris lumbricoides, cockroach, grass/tree pollen mix [31].”

Statistical analysis.

- **The analysis is based only on prevalence comparisons. If possible, I ask authors to adjust pooled prevalence for possible confounders (age, gender, city). Can cities be characterized in terms of demographic and socioeconomic indicators? If yes, please include these variables stratifying/adjusting for.**

Reply: This has been discussed above.

- **What was the proportion of missing data? Were the missing answers included or excluded in the prevalence computations?**

Reply: We included a “does not know/does not respond” option in the questionnaire, and assumed for analysis as a “NO” answer. In our data analysis, the frequency of this response option varied, but was below 3% for all questions in the questionnaire. This methodology has been used before by Rubin et al (http://www.jstor.org/pss/2291315); thus, they can be
considered ignorable missing. The calculations provided in the text and in the tables include this proportion of responses in the denominator of all prevalence estimates.

Results.

- **Authors identify some heterogeneity by age groups, gender and cities; how was this heterogeneity evaluated (ie. homogeneity test)?** Please check comments about heterogeneity because authors state “the prevalence of AE symptoms in the last 12 months varied little between cities or by age group” (page 9), while I see a pattern similar to that observed for asthma (page 8).

  Reply: We have decided to re-write the text in the “results” section using less conclusive vocabulary. We have also abstained from point by point statistical comparisons in prevalence estimates between conditions, age, sex and city; due to the large sample size, even minor differences tend to become statistically significant. We only show confidence intervals.

- **Authors found greater prevalence in children than in adults but they did not discuss these results...I advice to add this point to the discussion...**

  Reply: This has been done now. We have added a new paragraph in the discussion section, and added three additional references.

- **...Striking difference between prevalence from symptoms recording and from physician diagnosis; I advice to discuss potential explanations.**

  Reply: This has been done now in the discussion: “...in both surveys, the frequency of physician diagnosis is very low, when compared to symptom-based prevalence, suggesting lack of access to appropriate care.”

- **Clarify the numbers and the percentages in the third column of table 7.**

  Reply: This has been done now, we decided to only leave the percentages and explain this in the bottom of the table.

Discussion.

- **Provide an international comparison especially with respect to other developing countries, and to discuss differences and search for explanations.**

  Reply: This has been done now. Unfortunately, studies that have tried to assess prevalence of these diseases across age groups different from those evaluated in the ISAAC studies are few, and we found none from developing countries.

- **Authors discuss the increase was greater for AR than for asthma, but provide a reference from a Chinese study. Please add more references.**
Reply: This has been changed now: “The increase was greater for AR than for asthma, and this is in line with the ISAAC I-III comparisons in Latin America, where more centres had an increase for AR than for asthma [4].”

- **Proportion of kids not attending school.**

  Reply: Unfortunately, no accurate statistics could be found for Colombia. The proportion of kids in major urban cities (like the ones surveyed) not attending school, or with home schooling, is supposed to be very low.

  **Results of high prevalence of IgE exposure in the controls and the “helminths hypothesis” are very interesting but authors should recognize results are possible biased due to the selection bias as stated above.**

  Reply: We have now discussed the role of bias in a paragraph in the discussion. The selection bias postulated before by the reviewer, however, would have tended to decrease the observed prevalence estimate in controls.

- **It can be of interest if authors cite data supporting the hypothesis of a protective effect of helminth exposure on asthma...**

  Reply: We have abstained from postulating any association in the discussion. A protective effect of helminth exposure on the development of atopy has been described before in Latin America and elsewhere (Cooper PJ, Chico ME, Rodrigues LC, Strachan DP, Anderson HR, Rodriguez EA, Gaus DP. Risk factors for atopy among school children in a rural area of Latin America. Clin Exp Allergy 2004; 34: 845-852). The association with asthma is much less clear, but there is some evidence that helminth exposure increases hyperreactivity and asthma severity.

- **Authors should better define the study question providing more background about the time trend in prevalence worldwide and in developing countries, and possible explanations...**

  Reply: Given the limited focus now on formal comparisons between the two surveys over time (please see other reviewer’s comments), this component has been given less emphasis in the new version.

**Reviewer Prof. Sienra:**

Reply: We thank Professor Sienra for his positive review.