Author's response to reviews

Title: Systematic Review of Worldwide Variations of the Prevalence of Wheezing Symptoms in Children

Authors:

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Author's response to reviews: see over
15th August 2008

Dr Philippe Grandjean, Dr David Ozonoff,
Editors-in-Chief, *Environmental Health*

Dear Dr Grandjean, Dr Ozonoff

I enclose a revised copy of our article “Systematic review of worldwide variations of the prevalence of wheezing symptoms in children” for publication as a Review in *Environmental Health*. This revised copy has been updated following the three reviewers’ comments. An itemised set of responses to the referees’ comments is enclosed. We very much look forward to hearing from you as to the acceptability of the manuscript.

All correspondence should be with me, at the details given above. We look forward to hearing from you on our submitted revised our paper.

Yours sincerely

Mark Little

Enc

cc: Ms S Patel
    Professor M-R Järvelin
Response to the comments of referee 1 (Dirceu Solé) on “Systematic review of worldwide variations of the prevalence of wheezing symptoms in children” by S Patel, M-R Jarvelin and MP Little

This systematic review on “Worldwide variations of the prevalence of wheezing symptoms in children” is an extensive survey (during 16 years) of the published data about the prevalence of wheezing in children and adolescents. It is a very hard-working study, well-written and properly discussed.

The comparison of the published ISAAC trials and others studies that have applied the same asthma core written questionnaire but were not considered official centers of ISAAC, and those that did not use the ISAAC methodology were very interesting and in some way, intriguing. However, the data presented were similar to those previously observed worldwide. The ongoing efforts of time trends evaluation of the prevalence of wheezing in children and adolescents in UK and Australia is a limitation for this study. It would be more worthwhile if this systematic review was complemented by a meta-analysis (Revman 2.1) where data were gathered and examined by country and possibly by continent to allow the authors to obtain results not yet observed.

Agreed up to a point. We do not think that using Revman would materially change the results of our systematic review. It is simply a tool for doing such reviews. We have more or less done the analysis by country in those two countries where there is the most data (UK, Australia) and where such a meta-analysis if likely to be most productive. Doing a country-by-country analysis of the whole dataset would make the paper, which is already long, very much longer, and would possibly not much add to the take home message.

Page 4, paragraph 2 must be clarified, it does not make sense.
Agreed. We are slightly unsure what is unclear about this para, but have in any case revised it to attempt to clarify its meaning.

What next?: Accept after minor essential revisions
Response to the comments of referee 2 (Patrick Goodman) on “Systematic review of worldwide variations of the prevalence of wheezing symptoms in children” by S Patel, M-R Jarvelin and MP Little

I find this to be a well written and interesting paper.
I have the following MINOR ESSENTIAL REVISION Recommendations

ABSTRACT
In the abstract, first paragraph, say they reviewed "all studies published", this needs to be changed, they only considered studies meeting certain criteria (including population), so suggest some rewording
Agreed. We have modified this sentence.
the second last sentence in the results section, " In ISAAC studies....) this sentence doesn't read very well, again suggest a re-phrase.
Agreed. We have split this sentence, which we trust makes it more readable.

MAIN PAPER
(page 9) states the "USA had the largest number of published studies", on the same page it also states "Europe had the largest number of published studies overall", this needs to be clarified or altered.
Agreed. We have clarified this: we meant that of the North and South American countries the USA had the largest number of studies, but of the continental groups, the European studies were the most numerous.

DISCUSSION section
first sentence, states the authors reviewed "all epidemiological studies...", its possible some studies have been missed due to the selection criteria specified, so suggest that they use some other wording so as to not claim to have reviewed "all" papers.
Agreed. We have modified this sentence, very similar to the change made in the abstract.

The last paragraph of the discussion is very poor. I would recommend it be rephrased to clearly highlight the main conclusions/findings from this work (similar to the abstract)
Agreed, up to a point. We have somewhat shortened this para, to make it similar to the conclusions section of the Abstract. However, we feel it is important to briefly highlight what we feel to be the major strengths of the study (first sentence).
The tables 1-5 are all very large, and in the version of the paper reviewed appear over a number of pages, I'm assuming that any published version will be compacted for publication purposes, it would not be acceptable to have individual tables spread over many pages (or perhaps these could be available electronically to keep the paper short)
Agreed. This is largely up to the journal. We would be happy to have Tables 1-5 available in a supplementary Annex.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests
A systematic review of the prevalence of wheezing symptoms in children is presented by the authors of the present manuscript. Although most of the studies included are part of the ISAAC studies phase I and III, and are therefore well published in scientific literature, the authors added 127 additional studies that fulfilled specific quality criteria given in the manuscript. This addition makes sense and gives a better impression of the whole picture as it includes more rural study regions than ISAAC did. Furthermore the authors found major differences in ISAAC and non-ISAAC studies that are well-discussed in the manuscript. In addition to that a closer view is given on the differences of the prevalence of wheeze and its time-dependent development between UK and Australia. This is valid as there is significant migration between these countries and, on the other hand, definite climatic and cultural differences. Furthermore the data-density is high in both of these countries giving a good data-basis for comparisons.

There are a few points, though, that I think can be improved:

Abstract:
There is still a lot discussion about asthma, although the authors investigate wheezing symptoms which is not interchangeable with asthma. This should be better clarified.
Agreed up to a point. We have clarified in the background that wheezing is one of the symptoms of asthma. However, we make it fairly clear in what follows that we are concerned with wheezing, not asthma.

State in the method-part of the abstract, why ISAAC-studies are compared to non-ISAAC studies (to take into account regional differences / methodological differences).
Agreed. As we now make clear in the Methods part, the point of using ISAAC vs non-ISAAC was in part as a way of expanding the power to examine time trends (the older studies tend to be non-ISAAC), but also to examine possible methodological differences between ISAAC and non-ISAAC questions.

Results-part: line 7: adjusting for all other factors: you can never adjust for ALL the factors.
Agreed. We substitute “various” for “all”.

Introduction:
p4, par 1: Same as for Abstract. I would not start with “asthma”.
Agreed up a point. We have changed the first sentence to make clear that the main symptom used in diagnosis of asthma is wheezing. However, we judge that it is important to mention asthma, which is the underlying medical condition, as well as its principal symptom, wheeze. The logic of the Background section is fairly clear, moving from discussion of the variability in methods of diagnosis of asthma (paras 1-2), to its assessment in epidemiological studies, in particular via assessment of wheeze (paras 3, 4).

p4, par 4: The symptom of wheeze is rarely a sign of emphysema or chronic bronchitis in children. But it is very often a symptom of acute viral infection, which is really common in this age group. Please state that.
Agreed. We have concluded this para with a sentence to this effect.

p5, par 1: add a word about ISAAC Phase II.
Agreed. We have added a sentence to this effect.
p5, par 2, l 3: “all” non-ISAAC studies: all available non-ISAAC studies that fulfilled specific quality criteria
Agreed. We have made this substitution.

p5, par 2, l 12: In what follows….: very critical! you should never use “asthma” and “wheezing” interchangeably!
Agreed. We have clarified this sentence, to remove this ambiguity.

Methods:
p7, l15; age (yrs).: add “(years)” also in all the tables. The term in brackets (parental vs. self-report) must account for the prevalence, not the age, hopefully. Otherwise it does not make sense. Please change that also in the tables.
Agreed. The terms in brackets relate only to the method of ascertainment of wheezing, so of course nothing related to age; we combined these two separate items of information in the Tables only to save space. We have modified the table titles in line with the referee’s suggestion.

p8, par 2: statistics: please state the actual statistic model (formula) that you used. Although it is possible to use ratios (as prevalence) as an outcome parameter in a multiple logistic regression model this should be explained a bit more in detail.
Agreed. We now specify the model used at this point.

Results:
p11, par4, l2: “This shows a clear increasing trend...”. In my opinion this trend is obvious for the UK but not so for Australia, as there are only 2 studies done between 1970 and 1990.(Figure 1)
We disagree. We are not quite sure why the referee singles out this particular time interval, but overall (1990-2005) (which is what we were taking about, and now make clear) it is fairly clear from the figure that the prevalence increases in both countries.

Discussion:
p13, par 3, l 2: same as above: “all epidemiological studies”: see above, better write: all available studies, that fulfilled our quality criteria.
Agreed. We have modified this sentence to this effect.

p13, par4, l 5. Try to discuss these different findings in America. Can there be different migration- patterns accounting for the differences?
Agreed. We are slightly puzzled by this finding. As we point out, part of the explanation may be that at least Chile and Costa Rica, which are relatively developed countries, have many of the relevant characteristics of the US and Canada.

p15, par 2, l 2: Add: also in these countries, the ISAAC studies reported ...
Agreed. We have made this change.

p16, par 1, l 2: The multiple logistic regression analysis ... add: for the prevalence of wheezing ... was adjusted for..
Agreed. We have made this change.

p17, par 4: again, do not write “all studies” without explaining.
Agreed. We have modified this sentence.

Tables:
1-5: clearly state which of these are ISAAC and non-ISAAC studies. The footnotes A-H seem to be non-ISAAC, but it is not clear if all the others where ISAAC, or if they just used the ISAAC-questionnaire.
Agreed. We have now stated this clearly in the tables
Age: add “(years)” in table 2-5; P=parental/S=self reported # must be prevalence, not age.
Agreed. Done.
95% CI : remove “[ ]” brackets in the title and for all numbers (not necessary)
Agreed. Done.
“Turkey” is not part of the middle East but of Europe and Asia. It will be politically correct if you list the studies according to the main city they are performed.
Agreed up to a point. We have redesignated this Table (and the corresponding section in the main text) as Eastern Mediterranean and Africa.
It would be interesting to see a figure comparable to the ISAAC publications, for the prevalence of wheezing (for example for 6-12yrs old) in the different countries in the order of prevalence.
All this could be derived from the present Tables. We are not sure what benefit there would be in such an exercise, which would take quite some time.

Minors:
p 2, par 3, line 8: Australia showed “a” significantly higher prevalence
Agreed. Done.
p 4, par 2, line 4: different countries “will” also have # “can”
Agreed. Done.
p4, par 3, l 1: varying methods # different methods
Agreed. Done.
p5, par 1, l 3: “easy way” # “standardized method”
Agreed. Done.
p6, pt1. : typo: Embase DATABSES # databases
Agreed. Done.
p11, par2, l 1: Fiji had very high # had “a” very high
Agreed. Done.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.