Author's response to reviews

Title: Home Exposure to Arabian Incense (Bakhour) and Asthma Symptoms in Children: A Community Survey in Two Regions in Oman

Authors:

Omar A Al-Rawas (orawas@squ.edu.om)
Abdullah A Al-Maniri (almaniri@gmail.com)
Bazdawi M Al-Riyami (bazdawi@squ.edu.om)

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Author's response to reviews: see over
Dear Sir,

RE: MS: 5046163272194702 (Home Exposure to Arabian Incense (Bakhour) and Asthma Symptoms in Children: A Community Survey in Two Regions in Oman

Thank you for giving us the opportunity to respond to the reviewer’s comments on our revised manuscript. We have reviewed the comment of the reviewers and carefully studied all the points and observations raised by each of them. We were pleased to note that two the original three referees (referees # 2 and 3, Dr. David S. Chi and Dr. Yung-Ling Lee) were satisfied with the revised version with no additional comments, and the third (Referee #1; Dr. Hanaa Banjar) has only few additional suggestions which addressed. The manuscript was also reviewed from the statistical point of view by referee #4 (Dr. Giorgio Bedogni) in addition to a referee #5 (Dr. Girdhar Agarwal). All the points raised relating to data analysis and presentation were reviewed by the epidemiologist co-author (A. Al-Maniri).

Through carefully considering and addressing all the reviewers’ valuable comments, and revising the manuscript accordingly, we hope you will find the improved revised version acceptable for publication in BMC Pulmonary Medicine.

For easy reference to the reviewer’s comments, we inserted our responses (black text) immediately after each relevant comment (red text) in the following document.

Looking forwards to hearing from you

Regards,

Dr. Omar Al-Rawas

Corresponding Author
Re: RE: MS: 5046163272194702
Title: Home Exposure to Arabian Incense (Bakhour) and Asthma Symptoms in Children: A Community Survey in Two Regions in Oman

Reviewer’s Comments (Red and Green text) and our response (black text)

Referee #1: Hanaa Banjar

Major Compulsory Revisions:

In the abstract, the background paragraph: needs to add the aim of the study as mentioned and corrected in the introduction “whether exposure to bakhour contribute to the prevalence of asthma and its symptoms in Omani children by comparing two Omani regions with different prevalence of asthma”

R1.1 Agree, added as suggested

Discussion: is still very long and it could be shortened, the following paragraph can be deleted:
1. Pag 12, paragraph 2 “Several other studies from Asian populations, where different types of incense................ reported no significant difference in the use of bakhour between cases and control.(22)” as references have been mentioned and the comparisons were mainly for Arabian tradition or the Gulf areas and not China.

R1.2a: This information was given for the benefit of the reader and to highlight some contrasting findings in the association between incense burning and respiratory symptoms. In addition, the presented reports are consistent with our results in that although we did not find any association between asthma prevalence and exposure to bakhour, bakhour was a significant trigger of asthma symptoms. Nevertheless, we have now shortened this paragraph by deleting non essential details.

2. Page 13 paragraph 2 “The mechanisms by which bakhour provokes respiratory................. Incense burning has also been reported as a risk factor for elevated cord blood IgE.(12)” as the same findings were mentioned in the introduction.

R1.2b: Again this was to give some detail about this uncommon topic for the benefit of the reader. However, we agree with the reviewer that it is not essential and has been already mentioned in the introduction and therefore the sentence was deleted as suggested. As a result of this the last reference (ref # 23) was added to the relevant statement in the introduction and became ref # 15 with consequent arrangement of other references.
3. Page 13, paragraph 3 “In ISAAC studies, current asthma is defined by wheeze in the past 12 months (current wheeze)……. of asthma risk factors were evaluated”.

R1.2c: Although this information was already mentioned in Methods section, it was stated again in the discussion as part of addressing the study limitation. This point was particularly raised by referee #5 and we believe this statement is essential as deleting it will compromise the discussion of study limitation.

Title of figure 1 has been deleted needs to put it back and to add a legend to mention the value of the (star sign *).

R1.3: As per instructions to authors, the figure title and the legend which state the value of (*) were given in a separate page from the figure appearing to the reviewer as if they were missing!

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

R1.4: As mentioned previously, data analysis and presentation were performed by an epidemiologist (co-author). In addition, the manuscript was reviewed from statistical view by referee #4 with some comments that we have addressed (see under referee #4 please).

Referee #2: David S. Chi

It appears that all the concerns have been addressed.

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.

Referee # 4: Giorgio Bedongi

I was asked to review this paper as BMC statistical referee.

Major Compulsory Revisions
Abstract/methods: please, add that the study was performed in 2 cities with different prevalence of asthma.

R4.1: We agree with this comment which was similar to that of referee # 1 (see R1.1) and added as suggested. To clarify, they are two regions and not two cities.

Methods/subjects: the 2 regions (Muscat and South Sharqiyyah) were selected from a total of 10 cities which were in turn selected by stratified multi-stage sampling to be representative of Oman. I expect that sampling weights were used to ensure that. My question is: was there any need to use such weights to ensure that the studied schools were representative of *all* schools of Muscat and South Sharqiyyah?

R4.2: As indicated in Methods section, the two regions were purposely selected. Muscat was selected as representative of all regions in Oman. South Sharqiyyah was selected because it had the highest rate among all regions in Oman. The overall aim of ISAAC was to compare the risk factors of asthma between children in the two regions. There was no sampling weight, the schools were our sampling units and they were selected based on a multistage sampling to have a representative sample from each region. The representativeness is important especially for Muscat as the sample from Muscat is supposed to resemble a national sample, as stated in the methods.

Methods/subjects: the fact that the population of Muscat “comes from most regions of the country” is not important here because the original study (ISAAC) sampled it to be representative of whole Oman with other 9 countries (regions within Oman not countries).

R4.3: We agree with the reviewer that the original ISAAC study included all other regions. However, in phase II the sample was taken from only two regions. Muscat was selected because it has a prevalence rate to the national while Sharqiyyah has the highest rate in the country. The aim of ISAAC phase II study in Oman was to compare children of these two regions in terms of many asthma risk factors, including the exposure to bakhour.

Methods/questionnaire: do you have validity and repeatability data for the Arabian version of the ISAAC questionnaire? It is even better if you have already published them. Nonetheless, please report them in the text (or write that they are not available).

R4.4: The Arabic translation of the original English version of ISAAC questionnaire followed ISAAC Questionnaire translation protocol which includes translation and back translation to English by two independent bilingual translators familiar with local terms used for asthma symptoms and this was verified by ISAAC International Data Center. The ISAAC questionnaire has been validated by in several languages including Arabic and very widely cited and used by researchers in this field world-
Methods/questionnaire: the coding of a key variable of the study, i.e. frequency of incense use, is surprising: never or rarely vs. 1-2 times per wk vs. > 2 times per wk. Wouldn’t it be more understandable to write: < 1 vs. 1-2 vs. 2? This could avoid subjective interpretation of “never” and “rarely”.

R4.5: We agree with the reviewer that would have been a better way to address the question to avoid the misinterpretation and ultimately misclassification. Nevertheless, we think our definition would still capture the intended measure of the exposure variable and non-differential misclassification of the exposure is not likely.

Methods/questionnaire: how do you expect that parents interpret the question “Does exposure to bakhour affect your child breathing”? I suppose that you want to capture something more than asthma here. More importantly, explain why you use 2 outcomes, i.e. “asthma” and “affected by bakhour” in your study. This is even more important if you consider that, according to your analysis, the predictors of the 2 outcomes are different.

R4.6: We agree with the reviewer that the study wants to capture something more than the association between bakhour and asthma. The aim of this question was also to explore whether exposure to bakhour “triggers” asthma symptoms regardless of being a risk factor for developing asthma itself. So we had two hypotheses one is whether bakhour exposure is a risk factor for developing asthma i.e. asthma is the outcome, and the second was whether bakhour exposure is a trigger for asthma symptoms. This has now been explicitly expressed in the abstract and statement of the aim at the end of the introduction “The aim of this study was to explore whether exposure to bakhour contributes to the prevalence of asthma and/or triggers its symptoms in Omani children by comparing two Omani regions with different prevalence of asthma”.


Methods/questionnaire: which modifications did you do to the original ISAAC questionnaire list? Did you just add bakhour use? Please, provide validity and reliability data for the items you added to the list.

R4.7: Yes bakhour use variables were the only modifications made to the original questionnaire. The validity was assessed by face validity by the research team. Chronbach’s alpha, as measure of reliability, was 0.64 for these questions which is fairly good if we take into considerations that these are newly addressed questions. Validity and reliability information are now mentioned in the method section and also mentioned in the limitation of this study in the discussion section.

Methods/outcome measures: your definition of asthma is composite: 1) wheezing in the past 12 months or 2) ever had asthma + other core asthma symptoms. This makes your data not comparable to the ISAAC ones, which is not important for the aim of your study. However, this could make your data not comparable to those of other studies, including those of asthma risk factors, which is important for the aim of your study. Please, comment on this point in the discussion.

R4.8: We agree with the reviewer that our definition of "current asthma" is different from ISAAC study and possibly other studies that looked at similar risk factors. However, this is not unusual as there is no agreed definition for asthma in population surveys. Some use wheezing only like in ISAAC, others use self reported physician diagnosis of asthma, and some use combination of cardinal asthma symptoms. The important point is to explicitly describe the definition adopted and its rationale which we did. As we have stated in the methods and again in the study limitation part of the discussion, we believe patients with past history of asthma and dry cough not related to cold and or exercise wheeze in the past 12 months are very likely to have current asthma. If we adopt the ISAAC definition, these children would be misclassified as not having current asthma. In fact ISAAC definition is limited to current wheezers (children who reported wheeze in the past 12 months), whereas our definition includes current wheezers as per ISAAC definition and other children who have self reported asthma diagnosis together with asthma symptoms other than wheeze in the past 12 month.

Table 1: “1-3” and “>3” wheezing episodes are part of the same variable. How did you take into account this fact when performing the Chi-squared test? Were these items evaluated separately or as part of the same variable as they should (and as was done with logistic regression)?

R4.9: Each of the categories was considered as a separate variable (like having 2 dummy variables in logistic regression) and was compared to the reference of none. So we computed two chi square tests.
Table 1: The prevalence of bakhour use is VERY high in both Muscat and South Sharqiyyah. There are 1241*0.915 = 1136 children in Muscat and 1200*0.91 = 1092 in South Sharqiyyah exposed to bakhour. The power to detect a difference of 0.915 vs. 0.910 at alpha = 0.05 with n = 1200 per group is VERY low: 0.22. Thus, although the outcome (asthma prevalence) is unevenly distributed by design in the 2 cities (regions), this is not for the main predictor. Please, comment on this fact and discuss how it is expected to influence your results.

R4.10: As the use of bakhour is very common in Oman, we agree with reviewer that we didn’t have a power to detect the small difference at 0.05%. However, this variable, home exposure to bakhour was actually never used in the logistic regression analysis as a predictor. We used the other explanatory variables like frequency of bakhour and whether child was affected by bakhour exposure. As it can be seen from table 1, there are LARGE differences between the two regions in those variables and the sample size and the power are HIGH enough to detect the observed difference. In addition, based on the prevalence obtained in ISAAC phase one, the estimated and recommended sample size by ISAAC Phase Two Protocol to detect differences between centers in the prevalence of asthma and its symptoms was 1000 children per center. A sample of 1000 children per center including 100 wheezy children per center has a 90% power to detect a difference of wheezing between any centers of 6% vs. 10% at 5% significance level. In our study, the sample size in Muscat was 1241 (including 115 wheezy children), and in South Sharqiyyah it was 1200 (190 wheezy children).

Table 1: “<1”, “1-2” and “>2” times per wk are part of the same variable. How did you take into account this fact when performing the Chi-squared test? Were these items evaluated separately or as part of the same variable as they should (and as was done with logistic regression)?

R4.11: Each of categories was considered as a separate variable. As shown see in Table 1 “<1” is the reference value.

Your main conclusion relies on the accuracy of the frequency of bakhour usage so you must be very clear on this point (see also previous comment on coding of bakhour). Personally, I would trust more the fact that at multivariable analysis, bakhour usage was NOT associated with asthma prevalence (despite the clear fact that there is very low power to detect this effect). The clinical relevance and accuracy of reporting of this outcome is in fact higher that that associated with the “child affected by bakhour” outcome. To put your results into context, you should nonetheless compare your study to other studies using the SAME outcomes. Do they exist for “child affected by bakhour” outcome?

R4.12: The reviewer concern is relevant. However, in the absence of a clear cut evidence that there would have been potential misclassification due to coding
problems, as we mentioned earlier, we argue that exposure was measured objectively. However, if any misclassification has happened in the first two categories it would be non-differential misclassification which may have made OR closer to the null. We agree with reviewer that multivariate analysis, given limitations of this study, has reflected no association between asthma and bakhour frequency and this has been made clear in the conclusion. With regard to the power, please see our response to a previous question. We agree with reviewer asthma as an outcome is important clinical outcome. Nevertheless, we foresee the clinical importance of “child being affected by bakhour” as well. It is clinically very important to know if bakhour exposure triggers asthma symptoms, to avoid using bakhour when asthmatic child is present. To our knowledge, this is the only study which has such an outcome and explores its association with asthma.

Table 2: give the list of the factors for which OR was adjusted. Table 3: give the list of the factors for which OR was adjusted.

R4.13: They are adjusted for the same variables in the table. We made this clear now in the table.

Table 4: add 95% confidence intervals to the prevalence of respiratory symptoms

R4.14: We agree with reviewer that 95%CI is very important to present in any estimated measure. However, we believe having 95% CI for each prevalence wouldn’t have any extra advantage keeping in mind our main objective of this table was to compare the percentages (proportions) rather than presenting an estimated prevalence which were then tested using chi-square and p-values were presented. We have now used the term percentages instead of prevalence to avoid confusion between estimation and statistical testing.

Minor revisions

Results: please, give the respondent rate separately for Muscat and South Sharqiyah.

R4.15: We agree with reviewer. The rates have now been included.

Results: please, add standard deviations to the mean values, e.g. 11 (2) years.

R4.16: We agree. It has now been added

Results: you speak of (known or potential) confounding variables. Please, discuss them BRIEFLY in the introduction making a SHORT review of the literature.
R4.17: We agree. This was originally provided but removed on the recommendation of the referees of the original version. Nevertheless a brief statement with reference is included in the introduction.

Methods/statistical analysis: preformed is performed.
Methods/statistical analysis: Chi-square is Chi-squared test (which variant?).
Methods/statistical analysis: multivariable is better than multiple (or multivariate) when referring to logistic regression.

R4.18: We agree. They have been changed now.

Discretionary Revisions

Although there is nothing intrinsically wrong in using logistic regression to model predictors of prevalence, especially when a case-control design is used, it must be clear that the odds ratios at prevalence > 5-10% are not synonyms of prevalence ratios.

R4.19: We agree with reviewer that OR should not be interpreted as Prevalence Ratio. We also agree that when the disease is not rare, OR tends to overestimate the RR and PR would be a better estimate of RR if some assumptions are met.

Referee # 5: Girdhar Agarwal

1. The primary outcome measures are defined as (i) Prevalence of current asthma and (ii) Parent’s response to question “Does exposure to bakhour affect child breathing?” In my view, there should be only one primary outcome measure. Every other outcome should be secondary. The reason is that the sample size is calculated on the basis of primary outcome. The authors have not talked about the sample size calculations in their article.

R5.1: We agree with reviewer that studies needs to have a defined primary outcome. Nevertheless, as this study is a large project, it wouldn’t be fair to waste resources and efforts made to measure only one primary outcome. It is also not reasonable to report another very relevant outcome in another paper. We argue that both outcomes in this paper are of equal importance from both clinical and public health perspectives. While it is important to explore burning bakhour as a risk factor for asthma development, it is of no less importance to explore if bakhour triggers asthma symptoms among already asthmatics children. We can’t ascertain that one outcome is subordinate to another. Moreover, the sample size is, indeed, an issue of concern as the reviewer correctly stated. Nevertheless, we had a relatively large sample size,
2441 subject, which permits us to do multiple comparisons, in fact there were only 2 in this study.

I am concerned about the definition of “Effect on child breathing”. This seems to be too subjective as it depends on parent’s response. It may vary from one parent’s judgment to another. This is very important as it will change the results.

R5.2: We understand the reviewer concerns about the validity of the measured outcome as it is only parent’s response and not actually observing the effect on the child. However, if one needs to be concerned about the subjectivity, then one should be concerned about the subjectivity of all questionnaire based surveys including all ISAAC study results. All the information in this very large multi-centre international and widely cited study has been ascertained from the parents or self reported by older children. As far as validity of the estimates is concerned we believe that any misclassification of the outcome would have been non-differential and with specific but less sensitive tool to measure the outcome, we may end up with an underestimated estimate (OR), holding other biases in control. In addition, we would like to stress here that the validity and reliability of this questionnaire have been tested in different language versions. The ISAAC Steering Committee has already published many reports on the results of this study where all outcomes as well as all risk factors were measured by parent’s response.

3. I have question on the other outcome “asthma” also. This is also evaluated by the parent’s response only and not substantiated by any clinical examination.

R5.3: Please see the above response.

In this study, there is no need to report the unadjusted odds ratios (Table 2 and Table 3). The authors are calling these to be simple logistic regression, which is inappropriate.

R5.4: We understand the point the reviewer is addressing with regard to tables 2 and 3. Actually, dropping the unadjusted OR should not be a problem for the authors. In fact it is much easier not to report the unadjusted OR. But from our experience and also many reviewers point of view, is that having unadjusted information won’t harm the study results but it gives extra information to the reader interested in how an estimate would change after controlling for a potential confounder. We therefore suggest keeping the unadjusted OR, but we would be prepared to remove them if this was preferred by the editor. With regard to use simple logistic regression, though it has been used frequently in the literature, we now use logistic regression to include both univariate and multivariate logistic regression analysis.

5. What is the difference between “Ever had asthma” and “Current asthma” (Table 1)? Are these two groups mutually exclusive or they may have common subjects?
R5.5: These terms were clearly defined in the methods section. “Ever had asthma” refers to the ISAAC question: **Has your child ever had asthma?** A positive response indicates a previous or current diagnosis of asthma. In ISAAC, the term “current” refers to the past 12 months. As we stated in the methods section, “current asthma” was defined as positive response to wheeze in the past 12 months or positive response to “ever had asthma” together with a positive response to exercise wheeze or night cough in the past 12 months”. It is clear from our definition of **current asthma** that those with ever had asthma and current symptoms have current asthma. Thus the two terms are not mutually exclusive.

6. What is the outcome variable for multiple logistic regression results in Table 2? This will decide the title of the Table. The title should be “Multiple logistic regression for identifying the risk factors of outcome variable”.

R5.6: The title is “Crude and adjusted Odds Ratio (OR) with 95% Confidence Intervals (CI) of the effect of current asthma and other variables on reporting that the child is affected by exposure to bakhour using univariate and multiple logistic regression analysis” The outcome is the reporting of child being affected by bakhour. We think the existing title gives more details information about the table. In addition, we think the suggested title may not receive the support of other reviewers as none of the 4 reviewers of this paper raised the need to revise this title. We therefore suggest keeping the title as it is.

7. Delete the column “unadjusted odds ratios” in Table 2.

R5.7: Please see the above response (R5.5)

For dichotomous variables, there is no need to show the odds ratio 1. Actually for each dichotomous variable, there is only one odds ratio. For example Corresponding to variable “gender”, in the column of “adjusted odds ratio”, it should be reported as 1.31 (1.07-1.61). There is no need to show value “1”.

R5.8: We agree with the reviewer that showing the odd ratio (OR) “1” is not essential as it has no interpretational meaning. The purpose of showing OR of “1” is to present the reference category for each variable and is common practice. Presenting the reference category allow the reader to makes a judgment on what would be the comparison group. Of course for gender it would be obvious that would be the opposite sex. We are sure that the reviewer would agree that showing a reference category would be of extreme importance for the reader interpretation of the table. Whether we write 1 or don’t write it shouldn’t be a problem. We therefore suggest to keeping it. However, we are prepared to remove “1” from the reference category if this was preferred by the editor.
In Table 2, the number of subjects under “bakhour use per week” is 2035, whereas the total sample size is 2041.

R5.9: This is because 7 parents didn’t respond to this question.

10. In Table 3, also change the title as done for Table 2 (See comment (6)).

R5.10a: See response (R5.6) to the previous similar comment.

Delete the column of unadjusted odds ratios and delete the value 1 in “adjusted odds ratios” column corresponding to dichotomous variables.

R5.10b: See our response (R5.8) to the previous similar comment

11. Some typographical errors:
(a) Result section, line 2: main age (SD)……mean age (SD)
(b) Table 1 (last-but-one line): Bakhour use the child room…..Bakhour use in Child room

R5.11: Thanks for the corrections. These have now been changed.