Author’s response to reviews

Title: A prospective cohort study of the association between drinking water arsenic exposure and self-reported maternal health symptoms during pregnancy in Bangladesh

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Version: 3
Date: 8 April 2014

Author’s response to reviews:

Reviewer #1: Nicola Cherry

1) Although the design is simple, the potential for biased responding is very appreciable as, at enrollment, women were told about the hazards of arsenic and advised about safe water options (not specified). They were then told the level of arsenic in their water supply. While ethically appropriate, the feedback of this information put the results of the study in question. This problem would have been very largely avoided by analyzing only symptoms reported at recruitment, before the arsenic results were known. Even this may not have entirely removed the problem as women may well have known if their normal water source had >50ug/l arsenic, as such wells may carry a red ‘unsafe’ marker, but the problem of bias might have been reduced (particularly if symptom elicitation preceded education about arsenic hazards).

Response: The reviewer raises a very good point about the potential for bias. As mentioned in the manuscript, we recruited this study population in areas that had active arsenic awareness campaigns. These campaigns describe arsenic as “a poison found in the ground water that causes diseases of the skin and other parts of the body.” We were consistent with this messaging in our consent form and describe arsenic as “a poison” and that the intention of our study was “to find out how arsenic is handled in the body of pregnant women and whether it is affecting your health or your baby’s health.” If a participant consented to be in the study, we administered the study questionnaires and if the participant requested that their water be tested for arsenic, a technician made an appointment to go to their home to conduct the field test. We have clarified these steps in the revised manuscript and believe the process developed in this study was ethical and
neutral towards specific symptoms (see page 7). Per the reviewer’s suggestion, we also re-analyzed the data to examine the cross-sectional association between arsenic and pregnancy symptoms at the time of enrollment (N=1458). This data was consistent with the prospective analysis. We have included the cross-sectional analysis as Supplementary Table 1 & 2 but opted to retain the prospective analysis in the main text of the manuscript because it is a more powerful study design. We also included another new restricted prospective analysis that only looked at live births (Supplementary Table 3). All analyses yielded consistent associations.

2) While use of quartiles of exposure may be statistically efficient, the boundaries used cannot be interpreted in terms of existing guidelines (or provide very useful data to establish new ones). The results (table 3) suggest that there is increased risk of nausea/vomiting in quartiles 3 and 4. Quartile 3 has concentrations from 2 ug/l to 30 ug/l (with a geometric mean of 9) and quartile 4 from 32-1,400 ug/l (with a geometric mean of 106). For this reader it would be much more informative to use breakpoints at WHO and Bangladesh guidelines (of 10ug/l and 50ug/l) with perhaps a further division at 100ug/l. This would also have increased the credibility of the results – it seems unlikely than a concentration of 2ug/l would carry an appreciable risk yet with the quartile boundaries the risk reported is barely distinguishable from that for an exposure exceeding 1000ug/l.

Response: We appreciate the reviewer’s suggestion to evaluate the relationship between maternal symptoms at different regulatory guidelines. We have included two new tables in the revised manuscript to explore these associations. Table 5 examines the association below/above 50 µg/L and Table 6 examines the association below/above 10 µg/L. These analyses yielded consistent results. We opted, however, to retain the use of quartiles as the primary means of evaluating the exposure-response relationship because it more accurately reflects the underlying distribution of the data.

3) I found tables 1 and 2 almost impossible to understand. The authors have chosen to display only percentages (without counts) and the percentage chosen is of the total rather than the row (or, less useful, column). What I want from this table is to know the % of women in each quartile of arsenic (say) that have nausea. It is not there. The counts (but not %) are given in table 3 so with a hand calculator I can work this out for the main effect (though not confounders) but the reader shouldn’t have to work quite so hard.

Response: Per your suggestions we have revised Table 1 & 2 to include the counts and provided the percentages of specific illnesses across the column to highlight the exposure-response aspect of each symptom by category of arsenic. This, combined with the counts, should make it easier for the reader to quickly review the data and extrapolate any information they want.

4) In tables 3 and 4 some results are shown in bold, others equally interesting or important are not. It would be helpful to be consistent. 5) I found the use of the terms controls and cases in these tables distracting. N yes/no would have been equally informative.

Response: We have reformatted Tables 3 & 4 per your suggestion.
5) The discussion of bias (paragraph 2 page 11) appears superficial given the gravity of the problem for this study (see comment 1 above).

Response: We have added to our discussion regarding the possibility of bias in the prospective analysis. The consistency of the prospective analysis with the Supplementary cross-sectional analysis also helps to re-assure that the potential for bias was less likely. It is possible that participants had tested their water for arsenic prior to our study and subsequently were more likely to report health issues but this would not explain why we observed an increased odds of symptoms below the Bangladesh drinking water regulations in water that is referred to as “arsenic free” even though it just means it contains less than 50 µg/L. We have also included additional test regarding the recruitment procedure (see our response to #1).

6) The review of the literature in the Introduction and Discussion is almost identical. If findings from the study have moved the topic forward it may be appropriate to revisit the literature review to say how. If not, simply delete.

Response: We have edited both sections to remove duplication and to further expand on how this study provides new evidence that arsenic exposure contributed to higher probability that a pregnancy woman would experience nausea and vomiting during pregnancy.

Reviewer #2 Mohammad Dr Parvez

1) Abstract: The authors should report and distribution of water arsenic (range and mean) of the study participants. Importantly, the quartiles of the arsenic levels need to be included while reporting an association between the exposure and outcome. Interestingly, a protective effect was noted in the second quartile of arsenic exposure.

Response: We agree with the reviewer’s suggestion. We revised the abstract to include the overall mean and standard deviation of arsenic in drinking water, as well as, the mean concentration of arsenic in each quartile. Due to the word limit imposed by the journal on abstract length, we could not include any other information to describe the arsenic exposure.

2) Methods: I see a large number of participants were ‘lost to follow-up’ within a short period of time which I consider a major problem of the study. In fact, a third of the participants were missing in the analysis. I expect authors will address this issue adequately and provide plausible explanation. I would like to suggest moving the ‘Arsenic exposure’ before ‘Self-reported symptom during pregnancy’ as the exposure should follow the outcome.

Response: We note that 13.4% (n=196) of the 1,458 participants enrolled in this study could not be followed throughout all four scheduled study visits. This left 1,262 participants whose data was included in this analysis. Perhaps the omission of the count data in the Tables (see comment #3 above) made it difficult to notice that all available data was used in the analysis? We hope that the revised tables make this clear and want to assure the reviewer that all available data was utilized. We would also like to point out that when we compared selected characteristics between those lost to follow up and those retained in the
sample (pg 10-11), there was no difference in age, arsenic exposure in drinking water, parity, BMI or maternal education. This information helps to support the generalizability of our retained sample.

Per the reviewer’s suggestion, we have moved the section describing the arsenic exposure before the section describing the self-reported symptoms during pregnancy.

3) Outcome of the study, ‘Self-reported symptom during pregnancy’: The paper should clearly describe the outcomes that were used for this analysis. It indicated that the study participants were asked about their experience on ‘severe morning sickness’, this needs to be clarified in this section. How the severity was defined? Were there separate questions for nausea and vomiting? Was it based on frequency? This is important because nausea and vomiting are common symptoms experienced by women during pregnancy.

Response: The questions that we asked the participants were described in the methods section (pg. 8). Specifically, participants were asked if they had experienced any severe nausea or vomiting (yes/no) during their pregnancy to date. These questions were asked at three scheduled visits so the recall periods were (conception # first visit at <16 weeks GA; 16 weeks GA # 28 weeks GA; and 28 weeks GA # birth with that questionnaire being administered within one month of delivery). This information was used to create a frequency of symptom report over the pregnancy. A little over a third of the participants (39.2%) reported that they had experienced nausea and vomiting during this pregnancy so it was a common complaint. (For the new cross-sectional analysis included in the Supplementary Materials, we only look at the data collected at the first visit in the entire cohort. At that first visit, 38.6% has experienced nausea and vomiting.) Unfortunately, we did not ask any information to gauge the severity of the nausea and vomiting during the study. Therefore, we have omitted the statement ‘severe morning sickness’ from the revised manuscript and only describe it only as ‘nausea and vomiting’.

4) Statistical analysis: It is not clear whether data from a single visit or all the follow-up visits were included in the analysis. It seems from the title that cohort analysis was conducted, thus HR would be more appropriate than OR.

Response: This analysis uses information from three questionnaires that were administered at the time of enrollment (first visit), at 28 weeks gestational age (second visit), and after delivery (fourth visit). We have clarified this in the revised manuscript. Also, we have included an additional Supplemental Analysis that looked at this data cross-sectionally at the time of enrollment in the entire cohort. We have also opted to continue to use odds ratios to describe the association between the exposure and outcome because we did not have time to event information.

5) Result: The author should consider reporting actual arsenic concentration rather than GM which is difficult to explain for policy purpose. In the tables, headers reads, case and control. Was this the analysis/study was this case-control or cohort analysis. If this was a cohort analysis as the title suggests, the headers need to be changed. I am not clear about the variables that were
adjusted in this analysis. The confounding variables used for analysis should be constant across all outcomes. If a different set of variables are used, it needs to be justified.

Response: We appreciate the reviewer’s comment and have revised the results to report means. We have also revised the headers in the tables to say “yes” and “no” regarding the symptoms rather than “case and control”. Below each table, we have included the list of the variables that were adjusted for in each analysis. We have also revised the results section to include the list of variables adjusted for in each analysis. Since each health symptom (outcome) was modeled independently, we opted to use a parsimonious model approach because we appreciate the simple modeling approach. As described in the statistical section, we only included additional covariates in the model if they were significantly associated with the outcome. We have clarified that we used a parsimonious approach in the statistical section (pg 10). We have also included additional text in the results sections and Table headers to describe which covariates were controlled for in the multiple logistic regression models.