Author’s response to reviews

Title: Maternal and birth cohort studies in the Gulf Cooperation Council countries: a systematic review and meta-analysis

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Maternal and birth cohort studies in the Gulf Cooperation Council countries: a systematic review and meta-analysis

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We would like to thank the editor and the reviewers for assessing our manuscript and for their valuable feedback and suggestions. We would be pleased to accommodate and address any further points that the editor or reviewers may find unsatisfactory. Please find below a point-by-point reply addressing each of the editor’s and reviewer’s comments.

REPLY TO EDITOR’S REVIEWERS’ COMMENTS

Reply to the Editor

Comment: Thank you for your submission to the journal. I have read the manuscript and have now received responses from two peer reviewers. I had some concerns similar to what the reviewers have expressed but I believe the comments can be addressed through a clearer presentation of the purpose and results of the systematic review. The main aspects that will need to be carefully considered will be
the explanation of how what was found was heavily concentrated on a subset of countries and how that might preclude regional estimates;

Reply: We thank the editor for the raised comments and concerns. We agree with the editor on the relevance of our findings to a subset of countries and it might preclude the generalizability of the findings to a broader region. We have already addressed this limitation on interpreting and the generalizability of our findings in the discussion section under the limitations (Lines 451-457). Nevertheless, we believe that our review still has a high potential to benefit researchers and public health policy makers in the GCC region.

Comment: to consider whether an updated search is warranted and could be easily incorporated into the results.

Reply: we appreciate the reviewers’ request and thank the editor for supporting such important request. We have now updated our literature search up to June 30 2019 instead of November 2017 and incorporated all changes in the manuscript. Indeed, the update was very useful in adding significant number of eligible cohort studies in our review. Thank you!. (Please refer to figure 1)

Comment: Note that one reviewer suggests adding additional databases as well. Though I don't believe there is evidence to suggest that, in general, adding additional databases would produce a change in conclusion and may not yield any additional evidence beyond what a citation/reference check would.

Reply: we thank the reviewer and the editor for suggesting searching more databases. We have now searched one more major database which the “Scopus” database. (Please refer to figure 1)
Overall, updating the search and searching one more database did change the direction of the presented results. An expert librarian advised that searching 5 key databases in addition to hand-searching bibliographies of eligible published studies would be quite enough to find studies of an advanced study design, the cohort design.

Comment: Where reviewers have concerns about the breadth or formulation of the question, assume that other expert readers of the published article would have similar concerns and think about how those questions/concerns might be addressed/alleviated through a careful and precise explanation of the aims and whether the findings were adequate for meeting those aims - perhaps carefully explaining where the gaps in research are like you might in a scoping review. I have added additional time for revision given the possibility that the review may need substantial changes.

Reply: we thank the reviewer and the editor for the note. We have now modified our aims and reformulated our research objectives (Lines 98-103). We agree that identifying gaps in evidence would be addressed by a scoping review. However, we would like to highlight that our presented review has followed all the necessary and standard steps and guidelines to conduct and report systematic reviews and meta-analyses studies. Our review: First, addresses specific research objectives; second, registered on the PROSPERO for registration of systematic reviews, third, a peer-reviewed protocol was developed and published before conducting the present review, and fourth, our review was conducted and reported following the PRISMA guidelines for conducting and reporting systematic reviews. We believe that our presented review is much more comprehensive than a scoping review and it is eligible to be reported as a “systematic review and meta-analysis” study.
Reply to Reviewer #1:

Summary:
The authors review maternal and birth cohorts in countries of the Gulf Cooperation Council (GCC) up to November 2017. The principal conclusion is the need for more focus on environmental, medical, and biological exposures and outcomes relevant to the region. Compiling a list of maternal and birth cohorts in the GCC is useful for researchers interested in the region. It is also useful to have a summary of exposures and outcomes studied thus far, and a systematic assessment of risk of bias.

Reply: we appreciate the reviewer’s time and efforts in reviewing our work. We agree with reviewer that the principal conclusion is the need for more focus on environmental, medical, and biological exposures and outcomes relevant to the region. Additionally, in the revised manuscript, we have strengthened the conclusion part by adding implications for conducting and reporting of future cohort studies for better interpretation and applications (Lines 463-473).

Please find below a point-by-point reply addressing each of the reviewer’s comments. We would be pleased to accommodate and address any further points that the reviewer may find unsatisfactory.

Main Concerns:
1. the bulk of this manuscript is a scoping review rather than a systematic review. In so far as the review documents existing cohorts and assesses their risk of bias, the findings are useful. However, the main weakness is in the part of the review looking at the association of "common exposure-outcome pairs." A systematic review requires an a priori focused research question. the "PECO" outlined in this review is too general and is not, in my view, appropriate for a systematic review. For the reader to have confidence in the pooled estimates, the research question should be clear, and in turn, it would help the reader judge the appropriateness of inclusion/exclusion criteria and analysis methods. This is further supported by the fact that the findings of the meta-analysis appear to be irrelevant to the "Conclusions". The authors should consider including only the scoping review, while conducting systematic reviews and meta-analyses of focused research questions.

Reply: we thank the reviewer and the editor for the note. We have now modified our aims and reformulated our research objectives (Lines 98-103). We agree that identifying gaps in evidence would be addressed by a scoping review. However, we would like to highlight that our presented review has followed all the necessary standard steps and the established guidelines to conduct and report systematic reviews and meta-analyses studies. Our review: First, addresses specific research objectives; second, registered on the PROSPERO for registration of systematic reviews, third, a peer-reviewed protocol was developed and published before conducting the present review, and fourth, our review was conducted and reported following the PRISMA guidelines for conducting and reporting systematic reviews. We believe that our presented review is much more comprehensive than a scoping review and it is eligible to be reported as a “systematic review and meta-analysis” study.

2. The term "exposure" appears to refer to "main" exposures and well as to variables used for adjustment of confounding. This has implications for how associations in "exposure-outcome" pairs are interpreted. For example, treating "age" as a main exposure is different in interpretation than using it as a confounder. The paper does not seem to make this distinction. While this may not be problematic for the scoping exercise, I find it problematic for the interpretation of the meta-analysis.

Reply: we thank the reviewer for the comment. We agree with the reviewer on the raised example that treating "age" as a main exposure is different in interpretation than using it as a confounder. In cohort
studies many variables would be measured. In our review, we considered “exposure(s)” as the main exposure(s) as long as it is the main exposure where the cohort study was designed to investigate. For instance, if a cohort study was designed to look at the risk of maternal age on the development of GDM, where the magnitude of association (odds ratio) was adjusted for other variables such as BMI or parity, we were not interested on the adjusted odds ratio for the association between BMI and GDM or between parity and GDM, but we have considered adjusted estimates reporting strength of association between main “exposure” and “outcome”.

3. The upper time limit of the search is November 2017. Should this article be published, it would likely appear in 2019 or even 2020, meaning that the search would definitely need to be

Reply: we thank the reviewer for raising this comment. We agree on the importance of updating our review. We have now updated our literature search up to June 30 2019 including searching one more database (Please refer to Fig 1).

Some Specific Comments:

1. Line 39: weighted estimates of what?

Reply: we thank the reviewer for the comment. We have now made it clear what are the weighted estimates (Lines 40-42).

2. Line 42: clarify that "35" is the number of published studies that met inclusion criteria rather than the number of cohorts set up in the GCC.

Reply: we thank the reviewer for the comment. We have now clarified that the number “35” is the number of published studies included in our review (Line 44).

3. Line 84: what are examples of such "unique" exposures, and how were they addressed in the review?

Reply: we thank the reviewer for the comment. We have now replaced the word “unique” with “different” and provided some examples of exposures (Lines 80-81).

4. Lines 87-88: "health outcomes" is a neutral term, where the authors clearly mean "adverse health outcomes"; can also use "noncommunicable diseases and their risk factors"

Reply: we thank the reviewer for the comment. We have now made it clear that the “health outcomes” are the “adverse health outcomes” in particular the NCDs and their risk factors (Lines 83-84).

5. Line 178-179: Adjustment for the largest number of variables is not necessarily the most appropriate strategy for adjustment, and hence the estimates may not be the best representatives of the real estimate 6.

Reply: we thank the reviewer for the comment. We have now rephrased the sentence making it clear that the extracted estimates were the estimates that were adjusted for the likely potential confounders (Lines 157-159).
Line 225: significant typos

Reply: we thank the reviewer for spotting out those significant typos. We have corrected those typos and checked for other typos in the manuscript (Lines 203-205).

In conclusion, this is potentially a useful scoping exercise. However, it should be updated, and any SR/MA should be conducted on a priori focused research questions.

Reply: we thank the reviewer for the comment. We would like to highlight that our presented review has been updated till June 30 2019 as presented in Figure 1 and in the main text. As well as, as we have justified above, authors believe that this review is more comprehensive than a scoping review and it was designed, conducted, and reported as a systematic review and meta-analysis study following relevant guidelines for systematic reviews and meta-analyses studies.

Reply to Reviewer #1:

Comment: After carefully revising your manuscript "Maternal and birth cohort studies in the Gulf Cooperation Council countries: a systematic review and meta-analysis". I have a few concerns:

Reply: we would like to thank the reviewer for assessing our manuscript and for the raised valuable concerns and suggestions. Please find below a point-by-point reply addressing each of the reviewer’s concerns. We would be pleased to accommodate and address any further points that the reviewer may find unsatisfactory.

Concern: I don't think the conclusions drawn are sufficient to make a meaningful conclusion about all maternal and birth cohorts in Gulf Cooperation Council countries.

Reply: we thank the reviewer for the raised concern. We have now modified our conclusions to be in line with re-formulated research aims and objectives. Our conclusions should be read bearing in mind the raised limitations on the generalizability of our findings to all maternal and birth cohorts in Gulf Cooperation Council countries or to other countries. However, our conclusions are still informative in terms of identifying understudied exposures and in terms of advocating to improve the quality of analyzing and reporting of future cohort studies in the GCC countries.

Concern: I can see that the authors used only four databases (EMBASE, PubMed, Cochrana and Web of Science); these could not have been sufficient enough to yield all publications on maternal and birth cohorts. The authors may consider increasing the number of databases searched. Some of the other databases include: Scopus, Google Scholar, PsycINFO, Sociological Abstracts, etc. And regional databases in Arabic. Also the last search was done in November 2017, I believe this search is out of date.

Reply: we thank the reviewer for the raised concern. We have now increased the number of the searched databases as well as updated our search up to June 30 2019 instead of November 2017 (Please refer to Figure 1). We would like to highlight that an expert librarian advised that searching 5 key databases in addition to hand-searching bibliographies of eligible published studies would be quite enough to find studies of an advanced study design, the cohort design.
Concern: Almost 75% of the studies selected for inclusion in the systematic review (n=25, 71%) were conducted in two countries; i.e. Saudi Arabia and Kuwait. I believe this is not sufficient to warrant a systematic review on the birth and maternal outcomes in the selected region.

Reply: we thank the reviewer for the raised concern. We would like to make sure that we have not select any study to be included based on personal preference. We included all published maternal and birth cohort studies retrieved from the searched databases after careful and thorough screening following specific inclusion and exclusion criteria. Yes, we agree that majority of the cohort studies were in Saudi Arabia. Saudi Arabia is the largest country of the six GCC countries with larger number of academic and medical institutions as well as with couple of established and ongoing cohort studies such as the Riyadh Mother and Baby Multicenter Cohort Study (RAHMA) where there were so many of the included cohort studies in our review produced from this ongoing study. Actually, this is one of the main findings that calls for more cohort studies to be established in the other GCC countries.

Concern: I have concerns over the way the results of the systematic review are reported. The results appear more as a summary of the individual studies than results from a systematic review. I believe that a systematic review should go beyond merely summarizing the findings from individual studies selected.

Reply: we thank the reviewer for the raised concern. We agree with the reviewer that the results appear more as a summary of the individual studies. However, we would like to highlight that our presented review has followed all the necessary standard steps and the established guidelines to conduct and report systematic reviews and meta-analyses studies. Our review: First, addresses specific research objectives; second, registered on the PROSPERO for registration of systematic reviews, third, a peer-reviewed protocol was developed and published before conducting the present review, and fourth, our review was conducted and reported following the PRISMA guidelines for conducting and reporting systematic reviews. We believe that our presented review is much more comprehensive than a scoping review and it is eligible to be reported as a “systematic review and meta-analysis” study. To avoid confusion with scoping review, we have now modified our aims and re-formulated our research questions.

Specific comments: The annexes are unnecessarily long. I don't think all the details provided in the annexes are needed. The authors may find it helpful to summarize the data presented in the annexes into half of the current pages or even less.

Reply: we thank the reviewer for the raised specific comments. We have now considered producing new tables and much more shortened and informative annexes.