

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Maternal modifiable factors and risk of congenital heart defects: systematic review and causality assessment
AUTHORS	Gomersall, Judith; Moore, Vivienne; Fernandez, Renae; Giles, Lynne C.; Grzeskowiak, Luke; Davies, Michael; Rumbold, Alice

VERSION 1 – REVIEW

REVIEWER	Qu, Pengfei Northwest women's and children's Hospital, Translational Medicine Center
REVIEW RETURNED	20-Dec-2023

GENERAL COMMENTS	<p>This is a carefully done systematic overview study about CHD and the findings are considerable meaningful. A few minor revision are list below.</p> <ol style="list-style-type: none">1. The objective of the abstract part is too long and needs to be refined.2. The introduction section does not provide sufficient background information about the serious prevalence of CHD to help readers understand the significance of your research.3. There is an incomplete sentence on page 5, line 44 of method section. In addition, although the supplementary information has a detailed methods description, but the main body part of the method is too simple.4. The results section should be a presentation of the findings of this paper and not be confused with explanations of possible mechanisms that should appear in the discussion section.5. The strengths of the paper are not attractive enough, it would be helpful if you discussed the advantages of your paper more explicitly.
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REVIEWER	Yang, Li Guangzhou Women and Children's Medical Center
REVIEW RETURNED	09-Jan-2024

GENERAL COMMENTS	<p>The manuscript focuses on o reviewing associations between CHDs and maternal advanced age, obesity, diabetes, hypertension, smoking, and alcohol consumption, and assess causal nature of the associations through systematic overview with application of a Bradrod Hill criteria score-based causal assessment system. which may provide valuable insight for providing crucial insights into potential prevention strategies for CHDs. However, there are a number of issues that the authors will</p>
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	<p>need to clarify.</p> <p>1. In the methods of this manuscript, I suggest the authors put the part of the statistical analyses in the main manuscript rather than the supplementary material. The present methods of this manuscript is not complete.</p> <p>2. The presentation of the study's results in tabular format appears to occupy substantial space within the manuscript. Would it be feasible to represent these findings graphically instead? For instance, could Table 2 be effectively presented through a forest plot?"</p> <p>3. Figure S1 was not presented well which did not use a standard PRISMA Study Flow Chart, I suggest the authors revised this figure.</p> <p>4. The authors should clarify clearly about the publication bias of this manuscript.</p>
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REVIEWER	Saijo, Yasuaki Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine
REVIEW RETURNED	09-Mar-2024

GENERAL COMMENTS	<p>I think that this was a good comprehensive review of associations between CHD and maternal advanced age, obesity, diabetes, hypertension, smoking, and alcohol Consumption</p> <p>Major I consider that 'age' is not a modifiable factor. Please change the title.</p> <p>The prevalences for PAF calculation were not based on population studies. If global prevalences among women aged 18 to 50 were unavailable, their PAFS should not be calculated.</p> <p>Minor Results: There were lots of indentations.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Pengfei Qu, Northwest women's and children's Hospital

Comments to the Author:

This is a carefully done systematic overview study about CHD and the findings are considerable meaningful. A few minor revision are list below.

1. The objective of the abstract part is too long and needs to be refined.

We had included information about the context and motivation of our study/review in this "objective" section of the abstract due to the template not including a background section. To accommodate this request, we have removed one of the sentences relating to the motivation. The revised section of the abstract reads as follows: "Primary prevention strategies are critical to reduce the global burden of congenital heart defects (CHDs); this requires causal contributor knowledge. We aimed to review

associations between CHDs and maternal advanced age, obesity, diabetes, hypertension, smoking, and alcohol consumption, and assess causal nature of the associations”

2. The introduction section does not provide sufficient background information about the serious prevalence of CHD to help readers understand the significance of your research.

To address this comment, we have provided additional details about the significance of the CHD burden for afflicted individuals, families and society, and updated the references supporting the argument.

3. There is an incomplete sentence on page 5, line 44 of method section. In addition, although the supplementary information has a detailed methods description, but the main body part of the method is too simple.

Thank you for noting the error, which we have corrected (we removed the words “and the search strategies are provided in” in the last paragraph); we have extended the methods section and deleted the supplemental file with the methods.

4. The results section should be a presentation of the findings of this paper and not be confused with explanations of possible mechanisms that should appear in the discussion section.

We have not amended the manuscript to accommodate this suggestion as the mechanism explanations formed a key part of the Bradford Hill based assessment of the causal nature of associations undertaken to fulfil the objective of the paper.

5. The strengths of the paper are not attractive enough, it would be helpful if you discussed the advantages of your paper more explicitly.

We have added a sentence in the abstract and discussion to make it more explicit that the causal assessment aspect of the review, and related to this the signalling of priorities for CHD primary prevention is a key strength of the paper. This we had highlighted in the Article Summary section; we hope this ensures that the unique nature and high relevance for policy of this contribution is now easy to discern.

Reviewer: 2

Dr. Li Yang, Guangzhou Women and Children’s Medical Center

Comments to the Author:

The manuscript focuses on reviewing associations between CHDs and maternal advanced age, obesity, diabetes, hypertension, smoking, and alcohol consumption, and assess causal nature of the associations through systematic overview with application of a Bradford Hill criteria score-based causal assessment system. which may provide valuable insight for providing crucial insights into potential prevention strategies for CHDs. However, there are a number of issues that the authors will need to clarify.

1. In the methods of this manuscript, I suggest the authors put the part of the statistical analyses in the main manuscript rather than the supplementary material. The present methods of this manuscript is not complete.

We had included most of the information about methods in a supplementary file, to reduce word count. In response to this request, and other reviewer feedback we have removed the supplemental file with detailed methods and included all relevant information in the main body of the manuscript.

2.The presentation of the study's results in tabular format appears to occupy substantial space within the manuscript. Would it be feasible to represent these findings graphically instead? For instance, could Table 2 be effectively presented through a forest plot?"

We have not adjusted the text for this request as it will not be possible to present all the relevant data/results presented in the result Table 2 (or 3-5) in a forest plot, Specifically, the important sub-group information will no be clearly presented, considering the large number of reviews and results in the Tables. We also believe that the Tables with the results are not long, considering data commonly presented in a review such as the one being presented, and will be easy for the journal and users to digest.

3.Figure S1 was not presented well which did not use a standard PRISMA Study Flow Chart, I suggest the authors revised this figure.

We have not adjusted the PRISMA study flow chart as this is the usual chart used, with additional information which we provided to distinguish between records included and excluded after the initial and top up searches. The approach we have adopted helps to ensure that the flow chart serves its purpose, which is to make the study selection process transparent and replicable well.

4.The authors should clarify clearly about the publication bias of this manuscript.

We had discussed publication bias, in the abstract (very briefly) and discussion. Through this we thought that we had appropriately signalled the unknown level of this type of bias, which is usual in systematic reviews. However, to address this concern, we have amended the relevant sections, which now read as follows:

Abstract: "Unknown risk of publication bias is a limitation as reviews published in languages other than English and reviews in the grey literature were not eligible.

Discussion: "We did not access "grey literature" reviews which may contain smaller studies with null results not accepted for publication, and reviews not published in English (which may or may not exist) were not eligible. Most of the included reviews did not specifically search for "grey literature" studies, although most did assess publication bias (e.g., through use of funnel plots), and found no such bias"

Reviewer: 3

Prof. Yasuaki Saijo, Asahikawa Medical University

Comments to the Author:

I think that this was a good comprehensive review of associations between CHD and maternal advanced age, obesity, diabetes, hypertension, smoking, and alcohol Consumption

Major

I consider that 'age' is not a modifiable factor. Please change the title.

Scientific publications and pregnancy guidelines support the notion that age at pregnancy is a modifiable risk factor for congenital heart defects, and various other perinatal outcomes. We have not changed the title, as the intention in this review was to focus on maternal risk factors for CHDs that are modifiable.

The prevalences for PAF calculation were not based on population studies. If global prevalences among women aged 18 to 50 were unavailable, their PAFS should not be calculated.

We used global estimates of the prevalence of pregestational diabetes and obesity in the PAF calculations for these factors, which was clearly stated in the methods detailed in the supporting information. We have specified this clearly in the updated methods section of the main manuscript.

Minor

Results: There were lots of indentations. Noted.

VERSION 2 – REVIEW

REVIEWER	Qu, Pengfei Northwest women's and children's Hospital, Translational Medicine Center
REVIEW RETURNED	02-Jul-2024
GENERAL COMMENTS	The authors have revised their manuscript according to the comments I have indicated in my previous review. This study is recommended for publication.

VERSION 2 – AUTHOR RESPONSE