

## 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

<b>TITLE (PROVISIONAL)</b>	Burden, risk factors and outcomes of hyperemesis gravidarum in low- and middle-income countries (LMIC): systematic review and meta-analysis protocol
<b>AUTHORS</b>	Dinberu, Mesfin; Mohammed, Mohammed; Tekelab, Tesfalidet; Yimer, Nigus; Desta, Melaku; Habtewold, Tesfa

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Laila Tata University of Nottingham
<b>REVIEW RETURNED</b>	11-Oct-2018

<b>GENERAL COMMENTS</b>	<p>N.B. - the ticks above for 7 and 15 are very minor concerns and will be addressed in comments below:</p> <p>Overall comments:</p> <ul style="list-style-type: none"> <li>-Interesting and very needed study that will address a big gap in evidence</li> <li>-Minor edits to spelling/grammar/typo corrections are needed (hence 15)</li> <li>-The protocol does not appear on PROSPERO as stated in the manuscript, so this needs rectifying</li> </ul> <p>Abstract:</p> <ul style="list-style-type: none"> <li>-The aim of the review could be more specific in the abstract regarding outcomes – specifically in women and their children.</li> <li>-Very minor comment to make sure all is in future tense rather than past (i.e. we aim to)</li> </ul> <p>PECO:</p> <ul style="list-style-type: none"> <li>-Comment on 'E' - The review states that it is assessing risk factors for hyperemesis but the E specifies specific risk factors which are the main ones that have been found to be associated with hyperemesis, consistently or inconsistently across studies. I see that the search strategy does include 'risk factors' and it is likely best that the individual specified factors are searched for as well. I would suggest here for 'E' it should instead indicate that you are assessing any risk factors that are characteristics of the woman, including conditions before her pregnancy, as well as pregnancy and fetus related risk factors, rather than specifying a list (which could be presented somewhere else in the manuscript).</li> <li>-Comment on 'C' – The PICO/PECO does not always fit all studies ideally because its origin is for trials. The comparison of risk factors in women with hyperemesis to women without hyperemesis should be explicit (as it stands, it indicates that you are looking at the presence or absence of risk factors only within women with hyperemesis).</li> </ul>
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	<p><b>Eligibility criteria:</b>          The review will return many studies of women with hyperemesis that have no comparisons of women without hyperemesis. I think it will need some explanation as to how you are going to use these studies, such as whether they may be included in the burden if a measure is calculable, but excluded for the risk factor and outcome assessments. This again relates to the C-comparison, above.</p> <p><b>Data synthesis/analysis:</b>          It would be helpful to have some more specific separation of the methods for the 3 parts of the study (burden, RFs, outcomes) as these will be different (for example, the burden will be expressed in different ways for different studies). At the moment, it is quite a generic description.</p>
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<b>REVIEWER</b>	Jenny Cresswell London School of Hygiene & Tropical Medicine, UK
<b>REVIEW RETURNED</b>	30-Oct-2018

<b>GENERAL COMMENTS</b>	<p>Thank you very much for giving me the opportunity to review this paper. The protocol answers an appropriate and useful scientific question, and is generally clearly written. I have made a few suggestions below on areas in the protocol that I feel would benefit from additional clarification.</p> <p><b>INTRODUCTION</b></p> <p>Paragraph 1 - the authors describe a very substantial (5 to 10 fold) difference in the prevalence of HG between HICs and LMICs - but there is no comment on this or suggestion as to the possible explanations. The protocol would benefit from adding a sentence or two here outlining whether this the authors believe/hypothesise this to be a true difference (&amp; if so why) or whether it is due to data quality.</p> <p><b>METHODS</b></p> <p>Within the PECO criteria, under P: the authors should define LMIC...are they using the World Bank, or another set of criteria?</p> <p>Within the PECO criteria, under O: how is HG to be defined? Are self-reports acceptable? What are the specific diagnostic criteria? What will the authors do if a study gives vague diagnostic criteria?</p> <p>Search strategy: the MEDLINE database is a subset within PubMed, the authors shouldn't need to search both?</p> <p>Search strategy: the authors might want to consider including terms for LMICs within their search strategy (e.g. all the country names). This will make the search more targeted and I would expect would greatly reduce the number of citations, and thus workload, for the title/abstract screening stage.</p> <p>Search strategy: no mention of dates of the search is included as far as I could see. What is the time period for which studies are eligible? Note that the guidance from the Editors for protocol papers specifies that study dates should be included.</p>
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	<p>Eligibility criteria: it is important that the authors specify which study designs are eligible for the different parts of their question, this is currently unclear in the protocol. For example, whilst a case-control study may yield useful information on risk factors for HG it would provide no valid information on prevalence or burden and thus would need to be excluded for this part.</p> <p>Quality assessment: this section would benefit greatly from further development &amp; expansion. It is not clear how the reviews will rate the quality of evidence - the criteria to be used need to be expanded upon. The authors should also discuss Risk of Bias as distinct from study quality. The following paper may give some useful guidance, as may the Cochrane handbook: Katikireddi SV, Egan M, Petticrew M. How do systematic reviews incorporate risk of bias assessments into the synthesis of evidence? A methodological study. J Epidemiol Community Health 2015;69:189-195.</p> <p>Data synthesis: the authors make no mention as to how their quality assessment will be incorporated into the data synthesis &amp; analysis. It is important that they do so.</p> <p>Data synthesis: it may be beneficial to expand and develop the final sentence on narrative synthesis, as the reality is that this (high levels of heterogeneity precluding quantitative meta-analysis) is a likely scenario. It currently reads a bit as an afterthought to the statistical methods in terms of depth of explanation.</p> <p>OVERALL</p> <p>Minor editing is needed throughout: both for small grammatical errors, and there also seemed to be a number of instances where a space was missing.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Laila Tata

Institution and Country: University of Nottingham

Please state any competing interests or state 'None declared': None declared

Response: Thank you. Comment accepted and revised. (see page 12, line 9).

Please leave your comments for the authors below

N.B. - the ticks above for 7 and 15 are very minor concerns and will be addressed in comments below:

Overall comments:

-Interesting and very needed study that will address a big gap in evidence

Response: Thank you.

-Minor edits to spelling/grammar/typo corrections are needed (hence 15)

Response: Corrected.

-The protocol does not appear on PROSPERO as stated in the manuscript, so this needs rectifying.

Response: Thank you. The protocol already registered in the PROSPERO but the title is modified. Please see the link [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=96284](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=96284).

Abstract:

-The aim of the review could be more specific in the abstract regarding outcomes – specifically in women and their children.

Response: Thank you. We have amended in the revised manuscript. (See page 2, line 7).

-Very minor comment to make sure all is in future tense rather than past (i.e. we aim to)

Response: The comment accepted and Corrected. “With this systematic review and meta-analysis we aim to determine the prevalence/burden, risk factors, and maternal and perinatal outcomes of HG in low- and middle-income countries (LMIC)”. (see page 2, line 6)

PECO:

-Comment on ‘E’ - The review states that it is assessing risk factors for hyperemesis but the E specifies specific risk factors which are the main ones that have been found to be associated with hyperemesis, consistently or inconsistently across studies. I see that the search strategy does include ‘risk factors’ and it is likely best that the individual specified factors are searched for as well. I would suggest here for ‘E’ it should instead indicate that you are assessing any risk factors that are characteristics of the woman, including conditions before her pregnancy, as well as pregnancy and fetus related risk factors, rather than specifying a list (which could be presented somewhere else in the manuscript).

Response: Thank you. We have revised based on your comment “Exposure of HG includes any risk factors that are characteristics of the women including conditions before pregnancy, during pregnancy and fetal related risk factors”. (see page 6, line 15).

-Comment on ‘C’ – The PICO/PECO does not always fit all studies ideally because its origin is for trials. The comparison of risk factors in women with hyperemesis to women without hyperemesis should be explicit (as it stands, it indicates that you are looking at the presence or absence of risk factors only within women with hyperemesis).

Response: The comments accepted and the sentence amended. (see page 6, line 17).

Eligibility criteria:

The review will return many studies of women with hyperemesis that have no comparisons of women without hyperemesis. I think it will need some explanation as to how you are going to use these studies, such as whether they may be included in the burden if a measure is calculable, but excluded for the risk factor and outcome assessments. This again relates to the C-comparison, above.

Response: Clear inclusion and exclusion criteria included in the revised manuscript. (see page 7, line 15).

Data synthesis/analysis:

It would be helpful to have some more specific separation of the methods for the 3 parts of the study (burden, RFs, outcomes) as these will be different (for example, the burden will be expressed in different ways for different studies). At the moment, it is quite a generic description.

Response: Thank you. Data synthesis and analysis has been revised. (See page 9, line 14).

Reviewer: 2

Reviewer Name: Jenny Cresswell

Institution and Country: London School of Hygiene & Tropical Medicine, UK

Please state any competing interests or state 'None declared': None declared

Response: Thank you. Comment accepted and revised. (see page 12, line 9).

Thank you very much for giving me the opportunity to review this paper. The protocol answers an appropriate and useful scientific question, and is generally clearly written. I have made a few suggestions below on areas in the protocol that I feel would benefit from additional clarification.

Response: Thank you.

## INTRODUCTION

Paragraph 1 - the authors describe a very substantial (5 to 10 fold) difference in the prevalence of HG between HICs and LMICs - but there is no comment on this or suggestion as to the possible explanations. The protocol would benefit from adding a sentence or two here outlining whether this the authors believe/hypothesise this to be a true difference (& if so why) or whether it is due to data quality.

Response: We have mentioned the reason in the revised manuscript. "This might be due to the lack of uniform diagnostic criteria and unavailability of laboratory measurement, the higher percentages might be as a result of diagnosing a milder form of nausea and vomiting". (see page 4, line 10).

## METHODS

Within the PECO criteria, under P: the authors should define LMIC...are they using the World Bank, or another set of criteria?

Response: We have included the definition for LMIC in the revised manuscript. "LMIC will be identified according to the world bank new country classification by income level". (see page 6, line 13).

Within the PECO criteria, under O: how is HG to be defined? Are self-reports acceptable? What are the specific diagnostic criteria? What will the authors do if a study gives vague diagnostic criteria?

Response: Definition and diagnostic criteria included in the revised manuscript. "Hyperemesis gravidarum is the extreme/severe form of nausea and vomiting. To diagnosis HG, 2 certain clinical criteria should be met. These include pregnancy related, persistent nausea and vomiting not caused by other underlying medical conditions, ketonuria as a measure of acute starvation/dehydration, and at least a 5% (> 3 kg) weight loss from the pre-pregnancy weight". (see page 6, line 23).

Search strategy: the MEDLINE database is a subset within PubMed, the authors shouldn't need to search both?

Response: The comment accepted. (see page 7, line 5).

Search strategy: the authors might want to consider including terms for LMICs within their search strategy (e.g. all the country names). This will make the search more targeted and I would expect would greatly reduce the number of citations, and thus workload, for the title/abstract screening stage.

Response: The search strategy revised. We make it more specific ".....We will also include the names of LMICs in the search string". (see page 7, line 8).

Search strategy: no mention of dates of the search is included as far as I could see. What is the time period for which studies are eligible? Note that the guidance from the Editors for protocol papers specifies that study dates should be included.

Response: Date of search included in the revised manuscript. (see page 7, line 2).

Eligibility criteria: it is important that the authors specify which study designs are eligible for the different parts of their question, this is currently unclear in the protocol. For example, whilst a case-control study may yield useful information on risk factors for HG it would provide no valid information on prevalence or burden and thus would need to be excluded for this part.

Response: Eligibility criteria revised. We specified which studies to be included in the review. (see page 7, line 17).

Quality assessment: this section would benefit greatly from further development & expansion. It is not clear how the reviews will rate the quality of evidence - the criteria to be used need to be expanded upon. The authors should also discuss Risk of Bias as distinct from study quality. The following paper may give some useful guidance, as may the Cochrane handbook: Katikireddi SV, Egan M, Petticrew M. How do systematic reviews incorporate risk of bias assessments into the synthesis of evidence? A methodological study. *J Epidemiol Community Health* 2015;69:189-195.

Response: Thank you. A clear explanation has been given regarding the quality assessment. (See page 8, line 15, and page 9, line 1)

Data synthesis: the authors make no mention as to how their quality assessment will be incorporated into the data synthesis & analysis. It is important that they do so.

Response: Comment accepted and corrected in the revised document. (See page 10, line 8 & 15)

Data synthesis: it may be beneficial to expand and develop the final sentence on narrative synthesis, as the reality is that this (high levels of heterogeneity precluding quantitative meta-analysis) is a likely scenario. It currently reads a bit as an afterthought to the statistical methods in terms of depth of explanation.

Response:

The narrative sentence expanded.

"The Guidance on the Conduct of Narrative Synthesis in Systematic Reviews will be adapted to develop the synthesis. First, studies will be grouped and clustered based on their study design, setting (institution based and community based) and the nature of the results being reported. Then the characteristics of the included set of studies i.e. study details and participants, will be clustered together and reported in summary tables. The data for prevalence of hyperemesis will be presented separately according to the regions, based on LMIC classified by the world bank". (see page 10, line 8).

## OVERALL

Minor editing is needed throughout: both for small grammatical errors, and there also seemed to be a number of instances where a space was missing.

Response: Thank you. Corrected.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Jenny Cresswell London School of Hygiene & Tropical Medicine, UK
<b>REVIEW RETURNED</b>	11-Feb-2019

<b>GENERAL COMMENTS</b>	Thank you for addressing my comments. I am satisfied that everything has been addressed and happy to recommend the protocol be accepted for publication. Best of luck with the review.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Jenny Cresswell

Institution and Country: London School of Hygiene & Tropical Medicine, UK

Please state any competing interests or state 'None declared': None declared

Response: Thank you. Comment accepted and revised. (See page 12, line 9).

Please leave your comments for the authors below

Thank you for addressing my comments. I am satisfied that everything has been addressed and happy to recommend the protocol be accepted for publication. Best of luck with the review.

Response: Thank you very much.