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)	Impact of severe maternal morbidity on adverse perinatal outcomes in high income countries: Systematic review and meta-analysis protocol
AUTHORS	Mengistu, Tesfaye; Turner, Jessica; Flatley, Christopher; Fox, Jane; Kumar, Sailesh

VERSION 1 - REVIEW

REVIEWER	Azar Mehrabadi McGill University, Canada
REVIEW RETURNED	13-Dec-2018

GENERAL COMMENTS	This study is assessing the association between severe maternal morbidities (SMM) and adverse perinatal outcomes. SMMs are an important area of research because, as the authors mention, SMMs are more common than maternal deaths in high income countries, and can be targeted in order to prevent maternal deaths. The authors could improve the protocol by clarifying the rationale for the review of the association between SMM and perinatal death. Is their purpose of quantifying an association between SMM and adverse perinatal outcomes to (1) determine what proportion of perinatal outcomes could be prevented by eliminating SMM (2) determine whether SMM predicts adverse perinatal outcomes or (3) to simply see if there is an association? The reason it would be important to clarify the objectives is that if the authors are attempting to pursue goals #1 and #2, then it would be important to determine whether the SMM event temporally precedes the adverse perinatal outcome. In this case, in the limitations it should be acknowledge that it may be difficult to determine whether certain SMM events preceded some of the adverse perinatal outcomes. An example would be stillbirths where the stillbirth is not identified until following childbirth (and following a potential SMM). Another example would blood transfusion, which generally occurs following childbirth. In maternal blood transfusion outcomes, it is therefore unclear whether the blood transfusion caused the adverse perinatal outcome, whether it was completely unrelated to the adverse perinatal outcome or whether both SMM and adverse perinatal outcomes were cause by an underlying maternal illness. Perhaps as a way to address this problem, the authors could include some a priori hypotheses about specific SMMs and perinatal outcomes. As a minor revision, the authors should add a few sentences about how they will deal with papers that present the effect estimates from SMMs that are the main exposures versus effect estimates from confounders presented in the paper as confounding covariates in statistical models. It is generally accepted that they

	should only report the effect estimates for the main exposure (Westreich and Greenland 2013 Am J Epidemiol).

REVIEWER	Wendy Pollock The University of Melbourne and La Trobe University Australia
REVIEW RETURNED	13-Feb-2019

GENERAL COMMENTS	Congratulations on working towards an improved understanding of the impact of severe maternal morbidity on perinatal outcomes. See attached document for suggestions on improving your study protocol. This manuscript examines an important area of work – the impact of maternal critical illness on perinatal outcomes. It is a valuable piece of work and should be of interest to a large portion of the BMC Pregnancy and Childbirth audience. The study is a good idea and will highlight the limitations of our current understanding of the impact of severe maternal morbidity on perinatal outcomes. I think the research team is going to have some trouble conducting the study as it has been outlined in the protocol. For example, most papers reporting on severe maternal morbidity include women with multiple pregnancy, but the results are often not reported separately for singleton and multiple pregnancy; perinatal outcomes are often only reported descriptively and not as Odds Ratios. I suggest the protocol reflect these potential challenges and explain that if the planned inclusion and analysis methods stated are not feasible once the literature is examined, there may be a need to include studies and report on perinatal outcome descriptive statistics only. Also, the biggest confounding concern that is usually not accounted for in perinatal outcomes, is the influence of preterm birth (as often severe maternal morbidity and preterm birth co-exist) – the authors acknowledge this, but it is a significant problem. Need to add an apostrophe as weeks' gestation is short for weeks of gestation. Abstract: • Problem well stated and clearly communicated • Use consistent and universal terms — 'serious maternal morbidity (SMM)' – is used in the abstract whilst severe maternal morbidity (SMM) is used in the manuscript – prefer 'severe' as this is what is universally used • SMM continuum doesn't really start with 'normal maternal health outcomes' as there is no morbidity for those women – should change to 'minor complications' or some other description • In the methods section – good to include the years included in the search Introduction & background: • Provides a good background and overview of the broader issue of SMM • There is some inconsistency with your argument – in the last paragraph before your rationale, you state there is 'now some evidence' on the adverse perinatal outcomes, then in the rationale you state 'the impact on perinatal outcomes is less clear • Maybe include 'emerging evidence' instead of 'some evidence' in the last paragraph and emphasise that there has been limited exploration of the impact on perinatal outcomes in the rationale. 1

	Methods: • The organisation of the methods section is messy and needs re-organising • 'population, intervention/exposure/outcomes have been described prior to the 'methods and design' heading. • Suggest using the PRISMA checklist methods section to assist with structure of the methods information • Inclusion criteria: states that only studies which report SMM using the WHO criteria in singleton pregnancies over 20 weeks' gestation will be included – the WHO criteria are rather onerous and a number of studies have used 'WHO modified' criteria – also, the search list in Table 1 is not consistent with the WHO criteria (here you say it is 'based on' the WHO criteria– not sure what precisely you mean) • Exclusion criteria: in the selection of studies section, you state two further exclusions that are not listed under the exclusion criteria (management/treatment of SMM on perinatal outcomes & only studies which report OR/RR will be considered) – as indicated earlier – I think this latter exclusion will be too limiting and you may end up with no papers to include Discussion: • Limitations well out-lined. The duality of preterm birth and SMM is a significant concern. Conclusion: • Sensible Compulsory Revision 1. The methods section needs to be re-organised Discretionary Revision 1. Consider including the potential need for flexibility in the search terms, inclusion and exclusion criteria in the protocol, depending on the findings of the initial search. This iterative approach is acceptable according to the PRISMA statement.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Question #1: The authors could improve the protocol by clarifying the rationale for the review of the association between SMM and perinatal death.

Response #1: The rationale for this protocol has been revised and more information included. Please see the rationale section of the protocol.

Question #2: Is the purpose of quantifying an association between SMM and adverse perinatal outcomes to:

i. Determine what proportion of perinatal outcomes could be prevented by eliminating SMM

Response #2_i: The intention of this systematic review was not to determine the proportion of adverse perinatal outcomes that would be averted if SMM is eliminated/reduced to certain levels. From our preliminary review, studies on severe maternal morbidity have reported evidence gaps, methodological concern and absence of agreed definition for SMM to measure the attributable percentage of adverse perinatal outcomes due to SMM.

ii. Determine whether SMM predicts adverse perinatal outcomes

Response #2_ii: Yes. We planned to include studies which have used SMM as a determinant risk factor for adverse perinatal outcomes, with the intention to assess how SMM predicts adverse perinatal outcomes using effect estimates.

iii. To simply see if there is an association?

Response #2_iii: Yes. The purpose of the systematic review is to ascertain the association between SMM and adverse perinatal outcomes in HICs and summarise available evidence through presenting SMM risk factors of adverse perinatal outcomes, effect estimates/strength and directions of statistical associations to pinpoint the temporal association. This has been clarified in the objective section of the protocol. Regarding the temporality of SMM and adverse perinatal outcomes: although most SMM conditions precede adverse perinatal outcomes, some SMM conditions (eg. PPH followed by blood transfusion, hysterectomy) occur after child birth making the direct association with adverse perinatal outcomes less likely. Therefore, the authors acknowledge this as a potential limitation for the systematic review. Please see the strengths and limitations section.

iv. As a minor revision, the authors should add a few sentences about how they will deal with papers that present the effect estimates from SMMs that are the main exposures versus effect estimates from confounders presented in the paper as confounding covariates in statistical models. It is generally accepted that they should only report the effect estimates for the main exposure (Westreich and Greenland 2013 Am J Epidemiol).

Response #2_iv: Suggestion accepted, this has been included in the data extraction section of the protocol to read as: "….. key findings (effect estimates). Only the effect estimates of the main exposure variable (SMM) will be extracted and confounder variables used in selected studies will be presented separately".

Reviewer: 2-General Concern

Question #1: I think the research team is going to have some trouble conducting the study as it has been outlined in the protocol. For example, most papers reporting on severe maternal morbidity include women with multiple pregnancy, but the results are often not reported separately for singleton and multiple pregnancy

Response #1: We agree that this may be a potential issue as many studies that were conducted to assess the risk factors for SMM (not our study objective), referred to multiple pregnancy as a risk factor for SMM. However, in the majority of studies conducted to assess the association between SMM and adverse perinatal outcomes (aligned with our study objective), multiple pregnancies were excluded from analysis or adjusted in the models due to multiple pregnancy being a well-known risk factor for many adverse perinatal outcomes. Therefore, in our systematic review, studies which have included multiple pregnancies will be excluded, as indicated in the exclusion criteria.

Question #2: Perinatal outcomes are often only reported descriptively and not as Odds Ratios. I suggest the protocol reflect these potential challenges and explain that if the planned inclusion and analysis methods stated are not feasible once the literature is examined, there may be a need to include studies and report on perinatal outcome descriptive statistics only.

Response #2: Suggestion accepted. The inclusion criteria have been revised to include studies with sufficient data to calculate OR. The revised sentence reads as: "….studies which report odds ratio (OR), relative risk (RR) and studies which provide sufficient data to calculate risk estimates will be considered".

Question #3: Also, the biggest confounding concern that is usually not accounted for in perinatal outcomes, is the influence of preterm birth (as often severe maternal morbidity and preterm birth co-exist) – the authors acknowledge this, but it is a significant problem.

Response #3: Author agreement. In this protocol, we indicated that preterm birth is an assigned adverse perinatal outcome. The reviewer's concern is in line with our hypothesis that 'SMM is associated with adverse perinatal outcomes' including preterm birth. During the search, we identified studies which used PTB as either an outcome variable or a confounder variable. Therefore, we have included a statement indicating that confounder variables used in the included studies will be presented separately. Please, see the data extraction section.

Section specific reviewer's feedback

1. Abstract:

Question #1: Use consistent and universal terms — 'serious maternal morbidity (SMM)' – is used in the abstract whilst severe maternal morbidity (SMM) is used in the manuscript – prefer 'severe' as this is what is universally used

Response #1: Comment accepted, "severe maternal morbidity" has been used throughout the protocol.

Question #2: SMM continuum doesn't really start with 'normal maternal health outcomes' as there is no morbidity for those women – should change to 'minor complications' or some other description

Response #2: Comment accepted. We have revised the paragraph to read as: "Severe maternal morbidity (SMM) conditions are assigned to a continuum that ranges from minor maternal complications to contribution for maternal death".

Question #3: In the methods section – good to include the years included in the search

Response #3: comment accepted, we have indicated that "there was no restriction based on year of publication".

2. Introduction & background

Question #1: Provides a good background and overview of the broader issue of SMM

Response #1: We have limited the information due to word count requirements. However, we have revised the manuscript to provide a concise summary overview.

Question #2: There is some inconsistency with your argument – in the last paragraph before your rationale, you state there is 'now some evidence' on the adverse perinatal outcomes, then in the rationale you state 'the impact on perinatal outcomes is less clear

Response #2: The paragraphs preceding the rationale describes the rates of adverse perinatal outcomes. However, the statement in the rationale reflects the impact of SMM on adverse perinatal outcome. This has been reworded to distinguish these statements.

Question #3: Maybe include 'emerging evidence' instead of 'some evidence' in the last paragraph and emphasise that there has been limited exploration of the impact on perinatal outcomes in the rationale.

Response #3: Suggestion accepted. This has been changed in the manuscript.

3. Methods:

Question #1: The organisation of the methods section is messy and needs re-organising 'population, intervention/exposure/outcomes have been described prior to the 'methods and design' heading.

Response #1: The methods section has been revised to reflect your requested structure in addition to alignment with the PRISMA-P checklist. All these changes have been marked as track changes in the protocol.

Question #2: Inclusion criteria: states that only studies which report SMM using the WHO criteria in singleton pregnancies over 20 weeks' gestation will be included – the WHO criteria are rather onerous and a number of studies have used 'WHO modified' criteria – also, the search list in Table 1 is not consistent with the WHO criteria (here you say it is 'based on' the WHO criteria– not sure what precisely you mean)

Response #2: Many cited studies have used differing definitions of SMM (including the 'WHO modified' criteria). In this systematic review, our intention is not to overlook or exclude studies investigating the association with any of the maternal near-miss conditions and adverse perinatal outcomes, including studies conducted using composite measure. For this reason, we have created comprehensive search terms using specific near miss-conditions as listed on "The WHO near-miss approach for maternal health" document (URL:

https://apps.who.int/iris/bitstream/handle/10665/44692/9789241502221_eng.pdf?sequence=1&isAllowed=y) and/ or using generic free-text search terms (please see table 1 in the protocol). Please note that studies using the WHO modified criteria will be included as we will discern from those studies reflecting any near-miss conditions. However, as has been clearly indicated in the methods section, a

study will be ultimately excluded if it does not assess association of SMM with adverse perinatal outcome (in isolate or as a composite).

As the reviewers noted, the search terms listed in Table 1 appear to be inconsistent with the WHO criteria. In table 1, we have included the WHO maternal near-miss conditions and some generic terminologies (generic free-text search terms) which might be used by some studies to describe "severe maternal morbidity". For example, a study may have used "serious maternal morbidity", "obstetric near-miss" or "severe maternal complications" instead of "severe maternal morbidity" or any of the WHO near-miss conditions. We have used extensive search terms and synonymous terminologies to avoid missing studies which have used variant subject headings and titles. As recommended by Papaioannou D et al 2010, a comprehensive search using very broad search terms and search strategies is preferred when concepts and themes are poorly defined/ambiguous or variability exists (which is required for our study). Therefore, we revised the inclusion criteria (please see intervention section): "Severe maternal morbidity (SMM) will be the exposure variable. The list of WHO maternal near-miss conditions will be used to develop search terms. Variant terms and synonymous terminologies of severe maternal morbidity and maternal near-miss will also be used as generic free-text search terms (Table 1)."

Question #3: Exclusion criteria: in the selection of studies section, you state two further exclusions that are not listed under the exclusion criteria (management/treatment of SMM on perinatal outcomes & only studies which report OR/RR will be considered) – as indicated earlier – I think this latter exclusion will be too limiting and you may end up with no papers to include

Response #3: The exclusion criterion regarding studies done on the effect management/treatment of SMM on perinatal outcome has been moved to the exclusion criteria section and reads as: "Studies conducted to assess the effect of management/treatment of SMM on perinatal outcomes." The objective of this systematic review does not extend to assessing the effect of SMM management/treatment on adverse perinatal outcomes.

Including only studies which report OR/RR will limit the numbers of potentially eligible studies as it will exclude descriptive studies. Therefore, we revised this inclusion criterion under the study design/type section of inclusion criteria to read as: "Only studies reporting the association of SMM (using the WHO near-miss criteria) and adverse perinatal outcomes (either as a composite or separate) in singleton pregnancies >20 weeks gestation in HICs. The association should be presented as OR/RR estimates or provide sufficient information to calculate risk estimates".

Discussion:

Question #1: Limitations well out-lined. The duality of preterm birth and SMM is a significant concern.

Response #1: Comment accepted and addressed. Please see the limitation section of the protocol.

VERSION 2 – REVIEW

REVIEWER	Wendy Pollock La Trobe University, Australia The University of Melbourne, Australia
REVIEW RETURNED	10-Apr-2019

GENERAL COMMENTS	Thank you, I think the manuscript is much better with improved clarity. My only concern is that SMM papers often include women with multiple pregnancy and assisted conception in their population - so perhaps SMM papers limited to just those populations could be excluded & the issue of preterm birth and SMM is going to be hard to dissect. Best wishes with your search.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Wendy Pollock

Institution and Country: La Trobe University, Australia, The University of Melbourne, Australia

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

Please leave your comments for the authors below

Thank you, I think the manuscript is much better with improved clarity. My only concern is that SMM papers often include women with multiple pregnancy and assisted conception in their population - so perhaps SMM papers limited to just those populations could be excluded & the issue of preterm birth and SMM is going to be hard to dissect. Best wishes with your search. – We have carefully considered this but would prefer to include these two groups in for the time being. We will perform subgroup analysis and also be able to perform logistic regression to control for these confounders. We do not think that this will materially influence our results if appropriate statistical methods are applied and this issues carefully discussed as a limitation.