PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The role of maternal mental health disorders on stillbirth and infant mortality risk: A protocol for a systematic review and meta-analysis
AUTHORS	Adane, Akilew; Bailey, Helen; Marriott, Rhonda; Farrant, Brad; White, Scott; Morgan, Vera; Shepherd, Carrington

VERSION 1 – REVIEW

REVIEWER	David Ellwood Griffith University School of Medicine, Queensland, Australia and Gold Coast University Hospital. Queensland, Australia I am the co-Director of the NHMRC-funded Stillbirth Centre of Research Excellence (CRE) and as such I am involved in a large number of stillbirth-related studies. I have no direct or indirect involvement in any studies which might be seen to be competing with the aims of this study
REVIEW RETURNED	29-Dec-2019

GENERAL COMMENTS	Thanks for allowing me to review your study protocol. I believe it is a research question that is well worth asking and the methods proposed are appropriate. My only minor concern relates to the fact that you are proposing to study three different outcomes (stillbirth, neonatal death and infant mortality) which may have quite different causative pathways (accepting that there is some overlap between stillbirth and early neonatal death, and that some causes of infant mortality will have their origins in the perinatal period). I am not clear from the proposed methodology if the three outcomes of stillbirth, neonatal death or infant mortality are going to be looked at collectively or as individual, seperate outcomes? I think you should make it clear how you may deal with studies, some of which may look at just one outcome such as stillbirth, and others which will look at all causes of perinatal and infant mortality?

REVIEWER	Donald Dudley University of Virginia, USA
REVIEW RETURNED	09-Jan-2020

GENERAL COMMENTS	The paper by Adane, et al, describes a protocol for a systematic review and meta-analysis of maternal mental health disorders on stillbirth and infant mortality. Several issues need to be addressed: 1. Certainly having a stillbirth or infant death can certainly lead to adverse effects on maternal mental health. How can the authors

	determine cause from effect when considering maternal mental health disorders and stillbirth/infant mortality? 2. The authors note that the published literature is plagued by small numbers and different aspects are measured. The quality of a meta-analysis or systematic review is dependent on the quality of the studies included. Why would we expect this protocol lead to results of sufficient quality to be able to make any valid comments? 3. In the search strategy, what definition of stillbirth will be used? This is somewhat explained in the inclusion criteria, but the definition of stillbirth varies widely, so much so that studies are almost impossible to compare. This leads to a great deal of selection bias and makes interpretation of reviews and meta-analyses quite difficult. How will this be accounted for in the analytic plan? 4. Also in the search strategy, the authors will search studies published in the English literature since the inception of these databases without regard to year. Since these databases may extend several decades, how will the authors account for the changes in definition of depression and mental health disorders through progressive versions of the DSM? 5. In the data extraction, the authors note that any unsettled disagreement with be resolved by another member of the research team. However, this person is not specified and we have no idea as to whether this other member has the expertise to adjudicate any disputes. Please provide a more detailed description of how this would be managed. 6. In the quality and risk of bias assessment, the authors note the preference that they will have 10 or more studies included. This does not seem likely given their description of the current state of the literature. If there are not 10 studies, how will this bias assessment be affected?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: David Ellwood; Institution and Country: Griffith University School of Medicine, Queensland, Australia and Gold Coast University Hospital. Queensland, Australia

Please state any competing interests or state ‘None declared’:
I am the co-Director of the NHMRC-funded Stillbirth Centre of Research Excellence (CRE) and as such I am involved in a large number of stillbirth-related studies. I have no direct or indirect involvement in any studies which might be seen to be competing with the aims of this study

Please leave your comments for the authors below Thanks for allowing me to review your study protocol. I believe it is a research question that is well worth asking and the methods proposed are appropriate. My only minor concern relates to the fact that you are proposing to study three different outcomes (stillbirth, neonatal death and infant mortality) which may have quite different causative pathways (accepting that there is some overlap between stillbirth and early neonatal death, and that some causes of infant mortality will have their origins in the perinatal period). I am not clear from the

proposed methodology if the three outcomes of stillbirth, neonatal death or infant mortality are going to be looked at collectively or as individual, seperate outcomes? I think you should make it clear how you may deal with studies, some of which may look at just one outcome such as stillbirth, and others which will look at all causes of perinatal and infant mortality?
We appreciate the reviewer's comments. When sufficient data are available, random effects meta-analysis will be conducted for each child outcome (stillbirth, neonatal death and infant mortality) separately and collectively as a composite variable. We now have revised the analysis plan to reflect this.

Reviewer: 2
Reviewer Name: Donald Dudley; Institution and Country: University of Virginia, USA

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

Please leave your comments for the authors below The paper by Adane, et al, describes a protocol for a systematic review and meta-analysis of maternal mental health disorders on stillbirth and infant mortality. Several issues need to be addressed:

1. Certainly having a stillbirth or infant death can certainly lead to adverse effects on maternal mental health. How can the authors determine cause from effect when considering maternal mental health disorders and stillbirth/infant mortality?

We agree with the review that stillbirth or infant death can affect maternal mental health. Accordingly, to minimise reverse causality, we have restricted the scope of our study to prenatal maternal mental health disorders (diagnosed or reported prior to or during pregnancy) that occur prior to study outcomes.

2. The authors note that the published literature is plagued by small numbers and different aspects are measured. The quality of a meta-analysis or systematic review is dependent on the quality of the studies included. Why would we expect this protocol lead to results of sufficient quality to be able to make any valid comments?

Definitely, the quality of a systematic review and meta-analysis depend on included studies. However, we believe that systematic review provides strong and comprehensive evidence when individual studies do not provide a consistent picture on a subject of interest, particularly due to lack of statistical power.

3. In the search strategy, what definition of stillbirth will be used? This is somewhat explained in the inclusion criteria, but the definition of stillbirth varies widely, so much so that studies are almost impossible to compare. This leads to a great deal of selection bias and makes interpretation of reviews and meta-analyses quite difficult. How will this be accounted for in the analytic plan?

As there is no universally accepted definition for stillbirth, which varies across countries and settings, we will consider any fetal death at 20 or more weeks of gestation as a stillbirth. Depending on the definitions adopted by individual studies, a subgroup analyses (such as stillbirth between 20-27 weeks' gestation and 3rd trimester (≥28 weeks) stillbirth) will be conducted to assess whether the effect of maternal prenatal mental health differs across gestational age. We have now provided this detail on page 7.

4. Also in the search strategy, the authors will search studies published in the English literature since the inception of these databases without regard to year. Since these databases may extend several decades, how will the authors account for the changes in definition of depression and mental health disorders through progressive versions of the DSM?

We appreciate the reviewer's concern. As this review aims to provide comprehensive evidence and we anticipate a small number of studies in this area, we plan to not impose any limit based on year of publication. However, a range of subgroup and sensitivity analyses will be performed based on year of data collection, definition and types of maternal mental health disorders. We now have added this on page 7.

5. In the data extraction, the authors note that any unsettled disagreement with be resolved by another member of the research team. However, this person is not specified and we have no idea as to whether this other member has the expertise to adjudicate any disputes. Please provide a more detailed description of how this would be managed.

In this version, we have provided more descriptions and have specified the other authors who will help in resolving unsettled disagreements.

6. In the quality and risk of bias assessment, the authors note the preference that they will have 10 or more studies included. This does not seem likely given their description of the current state of the literature. If there are not 10 studies, how will this bias assessment be affected?

We have now rewritten this section and have provided more clarifications (Page 6, last paragraph). Indeed, we anticipate that there will be a small number of studies for this review and this will be a potential limitation for the actual review.

VERSION 2 – REVIEW

REVIEWER	David Ellwood Griffith University School of Medicine Queensland, Australia I am the co-Director of a national Centre of Research Excellence which is involved in multiple research projects on stillbirth investigations, audit and prevention strategies, and bereavement care.
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	Thank you for addressing the concerns of the reviwers

REVIEWER	Donald J. Dudley University of Virginia School of Medicine USA
REVIEW RETURNED	08-Mar-2020

GENERAL COMMENTS	My only concern about this revision is the relatively narrow definition of stillbirth to be employed in the analyses. By limiting the review to a definition of stillbirth after 20 weeks and in English will narrow the study somewhat. But I can live with this.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: David Ellwood

Institution and Country:

Griffith University School of Medicine

Queensland,

Australia

Please state any competing interests or state ‘None declared’:

I am the co-Director of a national Centre of Research Excellence which is involved in multiple research projects on stillbirth investigations, audit and prevention strategies, and bereavement care.

Please leave your comments for the authors below

Thank you for addressing the concerns of the reviewers

Action no required.

Reviewer: 2

Reviewer Name: Donald J. Dudley

Institution and Country:

University of Virginia School of Medicine USA Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below My only concern about this revision is the relatively narrow definition of stillbirth to be employed in the analyses. By limiting the review to a definition of stillbirth after 20 weeks and in English will narrow the study somewhat. But I can live with this.

We disagree with the reviewer that we are using a narrow definition of stillbirth by defining it as fetal death at 20 weeks’ gestation or more. This definition is wider than both the WHO definition of stillbirth (28 weeks’ gestation or more) or the definition used in the UK, (24 weeks or more). As we plan to perform meta-analyses, we needed to restrict the scope to studies with a similar definition, so we did not include pregnancy loss prior to 20 weeks.

In regards to the restriction to English language, we have already noted this as a potential limitation of this study. As no one in our team has the necessary proficiency, we cannot include other languages.