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The role of maternal mental health disorders on stillbirth and infant mortality risk: A protocol for a systematic review and meta-analysis

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Title

The role of maternal mental health disorders on stillbirth and infant mortality risk: A protocol for a systematic review and meta-analysis

Authors

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Keywords

Mental health disorders, depression, anxiety, stillbirth, infant mortality, systematic review

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ABSTRACT

Introduction: Maternal mental health disorders such as anxiety and depression are major public health concerns. Evidence shows a link between maternal mental health disorders and preterm birth and low birth weight. However, the impacts of maternal mental health disorders on stillbirth and infant mortality have been less investigated and inconsistent findings have been reported. Thus, using the available literature, we plan to examine whether prenatal maternal mental health disorders impact the risk of stillbirth and infant mortality.

Methods and analysis: This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). Systematic searches will be conducted in Medline, Embase, PsycINFO and Scopus for studies examining the association of prenatal mental health disorders and stillbirth and infant mortality. The search will be limited to studies published in English language and in humans only, with no restriction on the year of publication. Two independent reviewers will evaluate records and assess the quality of individual studies. The Newcastle-Ottawa scales and GRADE approach will be used to assess the methodological quality and bias of the included studies. In addition to a narrative synthesis, a random-effects meta-analysis will be conducted when sufficient data are available. I^2 statistics will be used to assess between-study heterogeneity in the estimated effect size.

Ethics and dissemination: As it will be a systematic review and meta-analysis based on previously published evidence, there will be no requirement for ethical approval. Findings will be published in a peer-reviewed journal and will be presented at various conferences.

Protocol registration number: PROSPERO (drafted submitted, record # 159834).

Strengths and limitations of this study

- To our knowledge, this systematic review will be the first to comprehensively synthesise and quantify the impact of maternal mental health disorders on stillbirth and infant mortality.
- Databases will be searched without time restrictions and independent evaluation will be employed.
- The methodological quality and risk bias of included studies will be evaluated using validated tools.
- The potential limitation of this review could be the heterogeneity of studies in exposure of interest and restriction to studies in English language.

INTRODUCTION

Perinatal death (stillbirth and neonatal death) remains a tragedy for many families around the world, including those in high-income countries, but because the risk factors are not fully understood[1-3] the rates of perinatal mortality, particularly stillbirth, have declined only slowly.[4] Prenatal maternal mental health disorders such as anxiety and depression are important public health concerns because of their high prevalence and their links to both short - and long-term adverse obstetric and child outcomes.[5 6] Maternal mental health disorders are one of the potential risk factors for stillbirth and infant mortality.[7-9] Meta-analytical evidence[10 11] has confirmed associations between maternal depression and anxiety and preterm birth and low birthweight, the leading causes of perinatal mortality.

Potential mechanisms linking maternal mental health disorders and perinatal morbidity and mortality may involve altered intrauterine environment and behavioural pathways. Women with mental health disorders are more likely to have poorer health seeking behaviour and are more likely to misuse illicit substances and drugs, which may further affect their health and capacity to manage all aspects of their pregnancy.[12 13] The intrauterine mechanisms are suggested to operate through disrupted placental functions because of hormonal changes (e.g., cortisol), inflammatory and physiological response.[14] However, the limited extant studies do not provide a consistent picture on the associations between maternal mental health disorders and stillbirth and infant mortality,[13] mainly because of the small numbers and/or because they measured different aspects of maternal mental health. Meta-analysis is a valuable approach to resolve inconsistencies across studies and provide high level of evidence, but, to our knowledge, there are no recent systematic reviews and meta-analyses which comprehensively evaluate the impact of mental health disorders on stillbirth and infant mortality risk. We found only one systematic review,[15] which evaluated the effect of maternal psychotic disorder on stillbirth risk, but not other common and less severe mental health disorders. The review was not specific to disorders occurring in the prenatal period and the authors acknowledged that all review studies (n=6) had important methodological limitations such as insufficient statistical power and not being population-based. Moreover, several papers[7-9 16-19] have been published in the area after this review. Given the high prevalence of maternal mental health disorders such as anxiety and depression, up-to-date and comprehensive evidence is required to inform policies and practice, and identify research gaps on the associations between prenatal maternal mental health disorders and early life mortality.

OBJECTIVES

This study aims to summarise the available evidence on the associations between prenatal maternal mental health disorders and stillbirth and infant mortality.

METHODS AND ANALYSIS

Search strategy

This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[20] Systematic searches will be conducted in four databases (Medline, Embase, PsycINFO and Scopus) from their inception to December 2019. This will be limited to studies published in English language and in humans only, with no restriction on the year of publication. Free texts and medical subject headings (MesH) terms related to maternal mental health disorders and early life mortality (stillbirth and infant mortality), tailored to each database, will be used to identify relevant literature. The reference lists and citations of the retrieved articles will be also checked manually for additional studies. Authors of individual studies will be contacted for additional information if required. The search strategies and terms for each database are included as a supplement file (Appendix A).

Eligibility criteria

Inclusion criteria: original case control, cohort or intervention studies will be included in the systematic review if they examined the association of any prenatal maternal mental health disorder (occurring prior to or during pregnancy) and stillbirth or infant mortality. We will include stillbirth (death of a fetus at 20 or more weeks of gestation or as defined by individual studies) and infant death (death of a liveborn baby in the first year of life). The association should be presented as odds ratios (ORs) or relative risks (RRs) estimates or there should be sufficient information to calculate either of these estimates.

Exclusion criteria: correspondence, theses, reviews, editorials, cross-sectional studies, case-only studies and conference abstracts will be excluded. Animal-only studies will also be excluded. If there are multiple publications reporting on the same cohort of women, the most recent and/or the largest by sample size will be included. Studies where it is unclear if the onset of the maternal mental health disorders was prior to birth will be excluded to minimise reverse causality.

Data extraction

All citations will first be imported into an Endnote library and duplicates will be removed. All records will be screened by their titles. All abstracts that pass the title screening will be uploaded to Rayyan (a systematic review application) and will be reviewed by two independent reviewers (AA and HB) based on the inclusion criteria. The full documents of the eligible abstracts will be further examined by the same authors. Finally, data on the list of authors, country and years of publication, study population, design, exposure and outcome assessment, association/s as well as confounders adjusted for will be extracted into a standardized Excel sheet. Data will also be extracted on other relevant characteristics such as maternal age, infant sex, birthweight, gestational age. At all stages, reviewers involved in the review will have face-to-face meetings to assess and resolve any disagreements on the review. Any unsettled disagreement will be resolved by another member of the research team who was not involved in the independent review process.

Quality and risk of bias assessment

The Newcastle-Ottawa quality assessment scales[21] will be used to assess the methodological quality of included studies. The tool assesses three major areas of a case control or cohort study which includes the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure (for case control studies) or outcome of interest (for cohort studies). The overall scores range from zero to nine; with low (scores between one and four), medium (scores between five and seven) or high quality (scores between eight and nine) grading. Risk of bias for each study will be assessed following the GRADE approach.[22] Two of the authors (AA and HB) will perform the independent quality and risk of bias appraisals. If sufficient number of studies are found, preferably 10 or more, funnel plot graphs will be used to asses risk of publication bias.[23]

Data synthesis

A systematic narrative synthesis will be conducted to describe the available studies, and when sufficient data are available, random effects meta-analysis will be conducted to obtain a pooled estimate with 95% confidence interval (CI).[24] Between-study heterogeneity will be tested using Cochran's Q test and will be further quantified using the index of heterogeneity squared (I^2) statistic.[25] The between-study heterogeneity will be considered as low (I^2=25%), moderate (I^2=50%) or substantial ($I^2 \geq 75\%$). If there is evidence of significant heterogeneity, the sources of this will be explored through

meta-regression and subgroup analyses. All the statistical analyses will be performed using STATA 15 (StataCorp, College Station).

Patient and public involvement

Patients and the public will not be involved directly in the design and conduct of the review.

ETHICS AND DISSEMINATION

As we will only analyse publicly available published data and we will not directly involve individuals, ethical approval is not required for this review. This systematic review protocol will be registered in the International Prospective Register of Systematic Reviews (PROSPERO). The findings of this review will be disseminated through publication in a peer-reviewed journal and scientific conferences and meetings. Effort will also be made to circulate findings through newsletters and media releases.

DISCUSSION

This systematic review and meta-analysis will comprehensively quantify the impacts of prenatal maternal mental health disorders on the risk on stillbirth and infant mortality. The findings will provide important information essential for practitioners and policymakers, identify research gaps in the literature and provide a foundation for future studies in this area.

Strengths and limitations

To our knowledge, this systematic review will be the first to comprehensively synthesise and quantify the impact of both severe and more common forms of prenatal maternal mental health disorders on stillbirth and infant mortality. The other strengths of this systematic review include the use of several databases with no time restrictions, and use of independent screening and evaluation. However, the review is anticipated to have some limitations. These include heterogeneity between studies in the exposure of interest and restriction to studies in English language, which may exclude important literature and compromise generalizability.

Contributors: AA, HB, and CS conceived the study and developed the search strategy. AA drafted the protocol. All authors critically revised the protocol for methodological and intellectual content and have read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

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Amendments of the protocol: If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

REFERENCES

1. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet (London, England)* 2011;377(9774):1331-40. doi: 10.1016/s0140-6736(10)62233-7 [published Online First: 2011/04/19]

2. Simpson LL. Maternal medical disease: Risk of antepartum fetal death. *Seminars in Perinatology* 2002;26(1):42-50. doi: https://doi.org/10.1053/sper.2002.29838

3. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)* 2016;388(10053):1725-74. doi: 10.1016/s0140-6736(16)31575-6 [published Online First: 2016/10/14]

4. Blencowe H, Cousens S, Jassir FB, et al. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. *The Lancet Global health* 2016;4(2):e98-e108. doi: 10.1016/s2214-109x(15)00275-2 [published Online First: 2016/01/23]

5. Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. *Obstetrics and gynecology* 2004;103(4):698-709. doi: 10.1097/01.AOG.0000116689.75396.5f [published Online First: 2004/03/31]

6. Fawcett EJ, Fairbrother N, Cox ML, et al. The Prevalence of Anxiety Disorders During Pregnancy and the Postpartum Period: A Multivariate Bayesian Meta-Analysis. *The Journal of clinical psychiatry* 2019;80(4) doi: 10.4088/JCP.18r12527 [published Online First: 2019/07/28]

7. Zhong Q-Y, Gelaye B, Fricchione GL, et al. Adverse obstetric and neonatal outcomes complicated by psychosis among pregnant women in the United States. *BMC pregnancy and childbirth* 2018;18(1):120.

8. Ban L, Tata LJ, West J, et al. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. *PloS one* 2012;7(8):e43462.

9. Nilsson E, Hultman CM, Cnattingius S, et al. Schizophrenia and offspring's risk for adverse pregnancy outcomes and infant death. *The British journal of psychiatry : the journal of mental science* 2008;193(4):311-5. doi: 10.1192/bjp.bp.107.045146 [published Online First: 2008/10/02]

10. Grote NK, Bridge JA, Gavin AR, et al. A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. *JAMA Psychiatry* 2010;67(10):1012-24. doi: 10.1001/archgenpsychiatry.2010.111

11. Ding XX, Wu YL, Xu SJ, et al. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. *Journal of affective disorders* 2014;159:103-10. doi: 10.1016/j.jad.2014.02.027 [published Online First: 2014/04/01]

12. Zuckerman B, Amaro H, Bauchner H, et al. Depressive symptoms during pregnancy: relationship to poor health behaviors. *American journal of obstetrics and gynecology* 1989;160(5 Pt 1):1107-11. doi: 10.1016/0002-9378(89)90170-1 [published Online First: 1989/05/01]

13. Surkan PJ, Patel SA, Rahman A. Preventing infant and child morbidity and mortality due to maternal depression. *Best practice & research Clinical obstetrics & gynaecology* 2016;36:156-68.

14. Khalifeh H, Brauer R, Toulmin H, et al. Perinatal mental health: What every neonatologist should know. *Early human development* 2015;91(11):649-53. doi: 10.1016/j.earlhumdev.2015.08.010 [published Online First: 2015/09/21]

15. Webb R, Abel K, Pickles A, et al. Mortality in offspring of parents with psychotic disorders: a critical review and meta-analysis. *American Journal of Psychiatry* 2005;162(6):1045-56.

16. Bitew T, Hanlon C, Kebede E, et al. Antenatal depressive symptoms and perinatal complications: a prospective study in rural Ethiopia. *BMC psychiatry* 2017;17(1):301. doi: 10.1186/s12888-017-1462-4 [published Online First: 2017/08/24]

17. Chen YH, Tsai SY, Lin HC. Increased mortality risk among offspring of mothers with postnatal depression: a nationwide population-based study in Taiwan. *Psychological medicine* 2011;41(11):2287-96. doi: 10.1017/s0033291711000584 [published Online First: 2011/04/29]

18. Goedhart G, Snijders AC, Hesselink AE, et al. Maternal depressive symptoms in relation to perinatal mortality and morbidity: results from a large multiethnic cohort study. *Psychosomatic Medicine* 2010;72(8):769-76.

19. Huang HC, Sung FC, Chen PC, et al. Obstetric outcomes in pregnant women with and without depression: population-based comparison. *Scientific reports* 2017;7(1):13937. doi: 10.1038/s41598-017-14266-3 [published Online First: 2017/10/27]

20. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097 [published Online First: 2009/07/22]

21. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. *http://www ohri ca/programs/clinical_epidemiology/oxford asp* 2001

22. Higgins JP, Altman DG. Assessing risk of bias in included studies. *Cochrane handbook for systematic reviews of interventions: Cochrane book series* 2008:187-241.

23. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. doi: 10.1136/bmj.d4002

24. Harris R, Bradburn M, Deeks J, et al. metan: fixed- and random-effects meta-analysis. *Stata Journal* 2008;8(1):3-28.

25. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557

Appendix A. databases and searching techniques

Medline (Ovid)

1. mental disorders/ or anxiety disorders/ or "bipolar and related disorders"/ or mood disorders/ or "p spectrum and other psychotic disorders"/ or substance-related disorders/
2. Depression/
3. (depression or anxiety or mental disorders or schizophrenia or psychosis).tw.
4. 1 or 2 or 3
5. Fetal Mortality/ or Child Mortality/ or Infant Mortality/ or Perinatal Mortality/
6. Infant Death/ or Fetal Death/ or Perinatal Death/
7. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
8. pregnancy outcome.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to (human and english language)

EMBASE (Ovid)

1. mood disorder/ or psychosis/ or schizophrenia spectrum disorder/
2. perinatal depression/ or depression/
3. anxiety/ or anxiety disorder/
4. (psychiatric disorder or mental disorder or mental disorders or psychosis or panic or schizophrenia or depression).tw.
5. 1 or 2 or 3 or 4
6. fetus mortality/
7. child death/
8. fetus death/ or stillbirth/
9. infant mortality/ or perinatal mortality/ or perinatal death/ or fetus death/
10. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
11. pregnancy outcome/
12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12
14. limit 13 to (human and english language)

PsycINFO (Ovid)

1. anxiety/ or panic attack/ or panic disorder/
2. affective disorders/ or anxiety disorders/ or bipolar disorder/ or chronic mental illness/ or psychosis/ or "substance related and addictive disorders"/
3. (depression or anxiety or mental disorders or schizophrenia or psychosis).tw.
4. 1 or 2 or 3
5. pregnancy outcomes/
6. Sudden Infant Death/
7. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to (human and english language)

Scopus

Will be used to search citations and references of relevant recorders identified from the three main databases.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7 & 1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health
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Methods and analysis: This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). Systematic searches will be conducted in Medline, Embase, PsycINFO and Scopus for studies examining the association of prenatal mental health disorders and stillbirth and infant mortality. The search will be limited to studies published in English language and in humans only, with no restriction on the year of publication. Two independent reviewers will evaluate records and assess the quality of individual studies. The Newcastle-Ottawa scales and GRADE approach will be used to assess the methodological quality and bias of the included studies. In addition to a narrative synthesis, a random-effects meta-analysis will be conducted when sufficient data are available. I^2 statistics will be used to assess between-study heterogeneity in the estimated effect size.

Ethics and dissemination: As it will be a systematic review and meta-analysis based on previously published evidence, there will be no requirement for ethical approval. Findings will be published in a peer-reviewed journal and will be presented at various conferences.

Protocol registration number: PROSPERO (drafted submitted, record # 159834).

Strengths and limitations of this study

- To our knowledge, this systematic review will be the first to comprehensively synthesise and quantify the impact of maternal mental health disorders on stillbirth and infant mortality.
- Databases will be searched without time restrictions and independent evaluation will be employed.
- The methodological quality and risk bias of included studies will be evaluated using validated tools.
- The potential limitation of this review could be the heterogeneity of studies in exposure of interest and restriction to studies in English language.

INTRODUCTION

Perinatal death (stillbirth and neonatal death) remains a tragedy for many families around the world, including those in high-income countries, but because the risk factors are not fully understood[1-3] the rates of perinatal mortality, particularly stillbirth, have declined only slowly.[4] Prenatal maternal mental health disorders such as anxiety and depression are important public health concerns because of their high prevalence and their links to both short - and long-term adverse obstetric and child outcomes.[5,6] Maternal mental health disorders are one of the potential risk factors for stillbirth and infant mortality.[7-9] Meta-analytical evidence[10,11] has confirmed associations between maternal depression and anxiety and preterm birth and low birthweight, the leading causes of perinatal mortality.

Potential mechanisms linking maternal mental health disorders and perinatal morbidity and mortality may involve altered intrauterine environment and behavioural pathways. Women with mental health disorders are more likely to have poorer health seeking behaviour and are more likely to misuse illicit substances and drugs, which may further affect their health and capacity to manage all aspects of their pregnancy.[12,13] The intrauterine mechanisms are suggested to operate through disrupted placental functions because of hormonal changes (e.g., cortisol), inflammatory and physiological response.[14] However, the limited extant studies do not provide a consistent picture on the associations between maternal mental health disorders and stillbirth and infant mortality,[13] mainly because of the small numbers and/or because they measured different aspects of maternal mental health. Meta-analysis is a valuable approach to resolve inconsistencies across studies and provide high level of evidence, but, to our knowledge, there are no recent systematic reviews and meta-analyses which comprehensively evaluate the impact of mental health disorders on stillbirth and infant mortality risk. We found only one systematic review,[15] which evaluated the effect of maternal psychotic disorder on stillbirth risk, but not other common and less severe mental health disorders. The review was not specific to disorders occurring in the prenatal period and the authors acknowledged that all review studies (n=6) had important methodological limitations such as insufficient statistical power and not being population-based. Moreover, several papers[7-9,16-19] have been published in the area after this review. Given the high prevalence of maternal mental health disorders such as anxiety and depression, up-to-date and comprehensive evidence is required to inform policies and practice, and identify research gaps on the associations between prenatal maternal mental health disorders and early life mortality.

OBJECTIVES

This study aims to summarise the available evidence on the associations between prenatal maternal mental health disorders and stillbirth and infant mortality.

METHODS AND ANALYSIS

Search strategy

This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[20] Systematic searches will be conducted in four databases (Medline, Embase, PsycINFO and Scopus) from their inception to December 2019. This will be limited to studies published in English language and in humans only, with no restriction on the year of publication. Free texts and medical subject headings (MesH) terms related to maternal mental health disorders and early life mortality (stillbirth and infant mortality), tailored to each database, will be used to identify relevant literature. The reference lists and citations of the retrieved articles will be also checked manually for additional studies. Authors of individual studies will be contacted for additional information if required. The search strategies and terms for each database are included as a supplement file (Appendix A).

Eligibility criteria

Inclusion criteria: original case control, cohort or intervention studies will be included in the systematic review if they examined the association of any prenatal maternal mental health disorder (occurring prior to or during pregnancy) and stillbirth or infant mortality. We will include stillbirth (death of a fetus at 20 or more weeks of gestation or as defined by individual studies) and infant death (death of a liveborn baby in the first year of life). The association should be presented as odds ratios (ORs) or relative risks (RRs) estimates or there should be sufficient information to calculate either of these estimates.

Exclusion criteria: correspondence, theses, reviews, editorials, cross-sectional studies, case-only studies and conference abstracts will be excluded. Animal-only studies will also be excluded. If there are multiple publications reporting on the same cohort of women, the most recent and/or the largest by sample size will be included. Studies where it is unclear if the onset of the maternal mental health disorders was prior to birth will be excluded to minimise reverse causality.

Data extraction

All citations will first be imported into an Endnote library and duplicates will be removed. All records will be screened by their titles. All abstracts that pass the title screening will be uploaded to Rayyan (a systematic review application) and will be reviewed by two independent reviewers (AA and HB) based on the inclusion criteria. The full documents of the eligible abstracts will be further examined by the same authors. Finally, data on the list of authors, country and years of publication, study population, design, exposure and outcome assessment, association/s as well as confounders adjusted for will be extracted into a standardized Excel sheet. Data will also be extracted on other relevant characteristics such as maternal age, infant sex, birthweight, gestational age. At all stages, reviewers involved in the review will have face-to-face meetings to assess and resolve any disagreements on the review. Any unsettled disagreement will be resolved by other members of the research team (CS and VM) who have expertise in the epidemiology of perinatal mental health issues and will not be involved in the independent review process.

Quality and risk of bias assessment

The Newcastle-Ottawa quality assessment scales[21] will be used to assess the methodological quality of included studies. The tool assesses three major areas of a case control or cohort study which includes the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure (for case control studies) or outcome of interest (for cohort studies). The overall scores range from zero to nine; with low (scores between one and four), medium (scores between five and seven) or high quality (scores between eight and nine) grading. Risk of bias for each study will be assessed following the GRADE approach.[22] Two of the authors (AA and HB) will perform the independent quality and risk of bias appraisals.

Funnel plots, a graphical illustration of effect estimates against their measure of precision (e.g., standard error), will be used to examine the risk of publication bias. In the absence of heterogeneity and bias, studies with high precision are plotted near the top of the funnel whereas studies with low precision are spread evenly on the bottom sides of the true effect, with the spread narrowing among larger studies with greater precision. Hence, asymmetry in funnel plots in the absence of heterogeneity may suggest possible publication bias, but when a small number of studies are included, it may be hard to differentiate an asymmetric plot occurring because of publication bias from that due to chance.[23] As a result, an alternative robust meta-analytical technique will be considered to detect and evaluate the risk of publication bias.[24]

Data synthesis

A systematic narrative synthesis will be conducted to describe the available studies, and 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. Accordingly, pooled estimates with 95% confidence interval (CI) will be calculated.[25] Between-study heterogeneity will be tested using Cochran's Q test and will be further quantified using the index of heterogeneity squared (I^2) statistic.[26] The between-study heterogeneity will be considered as low (I^2=25%), moderate (I^2=50%) or substantial ($I^2 \geq 75\%$). If there is evidence of significant heterogeneity, the sources of this will be explored through meta-regression and subgroup analyses. Additionally, a range of sensitivity analyses, for example, based on stillbirth definition, maternal mental health disorder definition, types and severity, data collection period (year), design and quality of included studies, will be considered. All the statistical analyses will be performed using STATA 15 (StataCorp, College Station).

Patient and public involvement

Patients and the public will not be involved directly in the design and conduct of the review.

ETHICS AND DISSEMINATION

As we will only analyse publicly available published data and we will not directly involve individuals, ethical approval is not required for this review. This systematic review protocol will be registered in the International Prospective Register of Systematic Reviews (PROSPERO). The findings of this review will be disseminated through publication in a peer-reviewed journal and scientific conferences and meetings. Effort will also be made to circulate findings through newsletters and media releases.

DISCUSSION

This systematic review and meta-analysis will comprehensively quantify the impacts of prenatal maternal mental health disorders on the risk on stillbirth and infant mortality. The findings will provide important information essential for practitioners and policymakers, identify research gaps in the literature and provide a foundation for future studies in this area.

Strengths and limitations

To our knowledge, this systematic review will be the first to comprehensively synthesise and quantify the impact of both severe and more common forms of prenatal maternal mental health disorders on

stillbirth and infant mortality. The other strengths of this systematic review include the use of several databases with no time restrictions, and use of independent screening and evaluation. However, the review is anticipated to have some limitations. These include heterogeneity between studies in the exposure of interest and restriction to studies in English language, which may exclude important literature and compromise generalizability.

Contributors: AA, HB and CS conceived the study and developed the search strategy. AA drafted the protocol and tested the search strategies in consultation with a librarian. RM, BF, SW and VM provided advice on the protocol. All authors critically revised the protocol for methodological and intellectual content and have read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

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Amendments of the protocol: If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

REFERENCES

1. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011;377(9774):1331-40.
2. Simpson LL. Maternal medical disease: Risk of antepartum fetal death. Seminars in Perinatology 2002;26(1):42-50.
3. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1725-74.
4. Blencowe H, Cousens S, Jassir FB, et al. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2016;4(2):e98-e108.
5. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 2004;103(4):698-709.
6. Fawcett EJ, Fairbrother N, Cox ML, White IR, Fawcett JM. The Prevalence of Anxiety Disorders During Pregnancy and the Postpartum Period: A Multivariate Bayesian Meta-Analysis. J Clin Psychiatry 2019;80(4).
7. Zhong Q-Y, Gelaye B, Fricchione GL, Avillach P, Karlson EW, Williams MA. Adverse obstetric and neonatal outcomes complicated by psychosis among pregnant women in the United States. BMC pregnancy and childbirth 2018;18(1):120.
8. Ban L, Tata LJ, West J, Fiaschi L, Gibson JE. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PloS one 2012;7(8):e43462.
9. Nilsson E, Hultman CM, Cnattingius S, Olausson PO, Bjork C, Lichtenstein P. Schizophrenia and offspring's risk for adverse pregnancy outcomes and infant death. Br J Psychiatry 2008;193(4):311-5.
10. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. JAMA Psychiatry 2010;67(10):1012-24.
11. Ding XX, Wu YL, Xu SJ, et al. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J Affect Disord 2014;159:103-10.
12. Zuckerman B, Amaro H, Bauchner H, Cabral H. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet Gynecol 1989;160(5 Pt 1):1107-11.
13. Surkan PJ, Patel SA, Rahman A. Preventing infant and child morbidity and mortality due to maternal depression. Best practice & research Clinical obstetrics & gynaecology 2016;36:156-68.
14. Khalifeh H, Brauer R, Toulmin H, Howard LM. Perinatal mental health: What every neonatologist should know. Early Hum Dev 2015;91(11):649-53.
15. Webb R, Abel K, Pickles A, Appleby L. Mortality in offspring of parents with psychotic disorders: a critical review and meta-analysis. American Journal of Psychiatry 2005;162(6):1045-56.
16. Bitew T, Hanlon C, Kebede E, Honikman S, Fekadu A. Antenatal depressive symptoms and perinatal complications: a prospective study in rural Ethiopia. BMC Psychiatry 2017;17(1):301.
17. Chen YH, Tsai SY, Lin HC. Increased mortality risk among offspring of mothers with postnatal depression: a nationwide population-based study in Taiwan. Psychol Med 2011;41(11):2287-96.
18. Goedhart G, Snijders AC, Hesselink AE, van Poppel MN, Bonsel GJ, Vrijkotte TG. Maternal depressive symptoms in relation to perinatal mortality and morbidity: results from a large multiethnic cohort study. Psychosomatic Medicine 2010;72(8):769-76.
19. Huang HC, Sung FC, Chen PC, et al. Obstetric outcomes in pregnant women with and without depression: population-based comparison. Sci Rep 2017;7(1):13937.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
21. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. http://www. ohri. ca/programs/clinical_epidemiology/oxford. asp 2001.

22. Higgins JP, Altman DG. Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions: Cochrane book series 2008:187-241.
23. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
24. Stanley TD, Doucouliagos H. Meta-regression approximations to reduce publication selection bias. Res Synth Methods 2014;5(1):60-78.
25. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. metan: fixed- and random-effects meta-analysis. Stata Journal 2008;8(1):3-28.
26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed.) 2003;327(7414):557-60.

Appendix A. databases and searching techniques

Medline (Ovid)

1. mental disorders/ or anxiety disorders/ or "bipolar and related disorders"/ or mood disorders/ or "p spectrum and other psychotic disorders"/ or substance-related disorders/
2. Depression/
3. (depression or anxiety or mental disorders or schizophrenia or psychosis).tw.
4. 1 or 2 or 3
5. Fetal Mortality/ or Child Mortality/ or Infant Mortality/ or Perinatal Mortality/
6. Infant Death/ or Fetal Death/ or Perinatal Death/
7. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
8. pregnancy outcome.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to (human and english language)

EMBASE (Ovid)

1. mood disorder/ or psychosis/ or schizophrenia spectrum disorder/
2. perinatal depression/ or depression/
3. anxiety/ or anxiety disorder/
4. (psychiatric disorder or mental disorder or mental disorders or psychosis or panic or schizophrenia or depression).tw.
5. 1 or 2 or 3 or 4
6. fetus mortality/
7. child death/
8. fetus death/ or stillbirth/
9. infant mortality/ or perinatal mortality/ or perinatal death/ or fetus death/
10. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
11. pregnancy outcome/
12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12
14. limit 13 to (human and english language)

PsycINFO (Ovid)

1. anxiety/ or panic attack/ or panic disorder/
2. affective disorders/ or anxiety disorders/ or bipolar disorder/ or chronic mental illness/ or psychosis/ or "substance related and addictive disorders"/
3. (depression or anxiety or mental disorders or schizophrenia or psychosis).tw.
4. 1 or 2 or 3
5. pregnancy outcomes/
6. Sudden Infant Death/
7. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to (human and english language)

Scopus

Will be used to search citations and references of relevant recorders identified from the three main databases.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7 & 1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

The role of maternal mental health disorders on stillbirth and infant mortality risk: A protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Epidemiology
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Keywords:	EPIDEMIOLOGY, MENTAL HEALTH, PERINATOLOGY

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Title

The role of maternal mental health disorders on stillbirth and infant mortality risk: A protocol for a systematic review and meta-analysis

Authors

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Keywords

Mental health disorders, depression, anxiety, stillbirth, infant mortality, systematic review

Word count, 1608

ABSTRACT

Introduction: Maternal mental health disorders such as anxiety and depression are major public health concerns. Evidence shows a link between maternal mental health disorders and preterm birth and low birth weight. However, the impacts of maternal mental health disorders on stillbirth and infant mortality have been less investigated and inconsistent findings have been reported. Thus, using the available literature, we plan to examine whether prenatal maternal mental health disorders impact the risk of stillbirth and infant mortality.

Methods and analysis: This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). Systematic searches will be conducted (from database inception to December 2019) in Medline, Embase, PsycINFO and Scopus for studies examining the association of prenatal mental health disorders and stillbirth and infant mortality. The search will be limited to studies published in English language and in humans only, with no restriction on the year of publication. Two independent reviewers will evaluate records and assess the quality of individual studies. The Newcastle-Ottawa scales and GRADE approach will be used to assess the methodological quality and bias of the included studies. In addition to a narrative synthesis, a random-effects meta-analysis will be conducted when sufficient data are available. I^2 statistics will be used to assess between-study heterogeneity in the estimated effect size.

Ethics and dissemination: As it will be a systematic review and meta-analysis based on previously published evidence, there will be no requirement for ethical approval. Findings will be published in a peer-reviewed journal and will be presented at various conferences.

Protocol registration number: PROSPERO (drafted submitted, record # 159834).

Strengths and limitations of this study

- To our knowledge, this systematic review will be the first to comprehensively synthesise and quantify the impact of maternal mental health disorders on stillbirth and infant mortality.
- Databases will be searched without time restrictions and independent evaluation will be employed.
- The methodological quality and risk of bias of included studies will be evaluated using validated tools.
- The potential limitation of this review could be the heterogeneity of studies in exposure of interest and restriction to studies in English language.

INTRODUCTION

Perinatal death (stillbirth and neonatal death) remains a tragedy for many families around the world, including those in high-income countries, but because the risk factors are not fully understood[1-3] the rates of perinatal mortality, particularly stillbirth, have declined only slowly.[4] Prenatal maternal mental health disorders such as anxiety and depression are important public health concerns because of their high prevalence and their links to both short - and long-term adverse obstetric and child outcomes.[5,6] Maternal mental health disorders are one of the potential risk factors for stillbirth and infant mortality.[7-9] Meta-analytical evidence[10,11] has confirmed associations between maternal depression and anxiety and preterm birth and low birthweight, the leading causes of perinatal mortality.

Potential mechanisms linking maternal mental health disorders and perinatal morbidity and mortality may involve altered intrauterine environment and behavioural pathways. Women with mental health disorders are more likely to have poorer health seeking behaviour and are more likely to misuse illicit substances and drugs, which may further affect their health and capacity to manage all aspects of their pregnancy.[12,13] The intrauterine mechanisms are suggested to operate through disrupted placental functions because of hormonal changes (e.g., cortisol), inflammatory and physiological response.[14] However, the limited extant studies do not provide a consistent picture on the associations between maternal mental health disorders and stillbirth and infant mortality,[13] mainly because of the small numbers and/or because they measured different aspects of maternal mental health. Meta-analysis is a valuable approach to resolve inconsistencies across studies and provide high level of evidence, but, to our knowledge, there are no recent systematic reviews and meta-analyses which comprehensively evaluate the impact of mental health disorders on stillbirth and infant mortality risk. We found only one systematic review,[15] which evaluated the effect of maternal psychotic disorder on stillbirth risk, but not other common and less severe mental health disorders. The review was not specific to disorders occurring in the prenatal period and the authors acknowledged that all review studies (n=6) had important methodological limitations such as insufficient statistical power and not being population-based. Moreover, several papers[7-9,16-19] have been published in the area after this review. Given the high prevalence of maternal mental health disorders such as anxiety and depression, up-to-date and comprehensive evidence is required to inform policies and practice, and identify research gaps on the associations between prenatal maternal mental health disorders and early life mortality.

OBJECTIVES

This study aims to summarise the available evidence on the associations between prenatal maternal mental health disorders and stillbirth and infant mortality.

METHODS AND ANALYSIS

Search strategy

This systematic review and meta-analysis will adhere to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[20] Systematic searches will be conducted in four databases (Medline, Embase, PsycINFO and Scopus) from their inception to December 2019. This will be limited to studies published in English language and in humans only, with no restriction on the year of publication. Free texts and medical subject headings (MesH) terms related to maternal mental health disorders and early life mortality (stillbirth and infant mortality), tailored to each database, will be used to identify relevant literature. The reference lists and citations of the retrieved articles will be also checked manually for additional studies. Authors of individual studies will be contacted for additional information if required. The search strategies and terms for each database are included as a supplement file (Appendix A).

Eligibility criteria

Inclusion criteria: original cross-sectional, case control, cohort or intervention studies will be included in the systematic review if they examined the association of any prenatal maternal mental health disorder (occurring prior to or during pregnancy) and stillbirth or infant mortality. We will include stillbirth (death of a fetus at 20 or more weeks of gestation or as defined by individual studies) and infant death (death of a liveborn baby in the first year of life). The association should be presented as odds ratios (ORs) or relative risks (RRs) estimates or there should be sufficient information to calculate either of these estimates. In addition, individual studies should include at least one stillbirth/infant mortality case in both exposed and unexposed groups.

Exclusion criteria: correspondence, theses, reviews, editorials, case-only studies and conference abstracts will be excluded. Animal-only studies will also be excluded. If there are multiple publications reporting on the same cohort of women, the most recent and/or the largest by sample size will be included. Studies where it is unclear if the onset of the maternal mental health disorders was prior to birth will be excluded to minimise reverse causality.

Data extraction

All citations will first be imported into an Endnote library and duplicates will be removed. All records will be screened by their titles. All abstracts that pass the title screening will be uploaded to Rayyan (a systematic review application) and will be reviewed by two independent reviewers (AA and HB) based on the inclusion criteria. The full documents of the eligible abstracts will be further examined by the same authors. Finally, data on the list of authors, country and years of publication, study population, design, exposure and outcome assessment, association/s as well as confounders adjusted for will be extracted into a standardized Excel sheet. Data will also be extracted on other relevant characteristics such as maternal age, infant sex, birthweight, gestational age. At all stages, reviewers involved in the review will have face-to-face meetings to assess and resolve any disagreements on the review. Any unsettled disagreement will be resolved by other members of the research team (CS and VM) who have expertise in the epidemiology of perinatal mental health issues and will not be involved in the independent review process.

Quality and risk of bias assessment

The Newcastle-Ottawa quality assessment scales[21] will be used to assess the methodological quality of included studies. The tool assesses three major areas of a case control or cohort study which includes the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure (for case control studies) or outcome of interest (for cohort studies). The overall scores range from zero to nine; with low (scores between one and four), medium (scores between five and seven) or high quality (scores between eight and nine) grading. Risk of bias for each study will be assessed following the GRADE approach.[22] Two of the authors (AA and HB) will perform the independent quality and risk of bias appraisals.

Funnel plots, a graphical illustration of effect estimates against their measure of precision (e.g., standard error), will be used to examine the risk of publication bias. In the absence of heterogeneity and bias, studies with high precision are plotted near the top of the funnel whereas studies with low precision are spread evenly on the bottom sides of the true effect, with the spread narrowing among larger studies with greater precision. Hence, asymmetry in funnel plots in the absence of heterogeneity may suggest possible publication bias, but when a small number of studies are included, it may be hard to differentiate an asymmetric plot occurring because of publication bias from that due to chance.[23] As a result, an alternative robust meta-analytical technique will be considered to detect and evaluate the risk of publication bias.[24]

Data synthesis

A systematic narrative synthesis will be conducted to describe the available studies, and 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. Accordingly, pooled estimates with 95% confidence interval (CI) will be calculated.[25] Between-study heterogeneity will be tested using Cochran's Q test and will be further quantified using the index of heterogeneity squared (I^2) statistic.[26] The between-study heterogeneity will be considered as low (I^2=25%), moderate (I^2=50%) or substantial ($I^2 \geq 75\%$). If there is evidence of significant heterogeneity, the sources of this will be explored through meta-regression and subgroup analyses. Additionally, a range of sensitivity analyses, for example, based on stillbirth definition, maternal mental health disorder definition, types and severity, data collection period (year), design and quality of included studies, will be considered. All the statistical analyses will be performed using STATA 15 (StataCorp, College Station).

Patient and public involvement

Patients and the public will not be involved directly in the design and conduct of the review.

ETHICS AND DISSEMINATION

As we will only analyse publicly available published data and we will not directly involve individuals, ethical approval is not required for this review. This systematic review protocol will be registered in the International Prospective Register of Systematic Reviews (PROSPERO). The findings of this review will be disseminated through publication in a peer-reviewed journal and scientific conferences and meetings. Effort will also be made to circulate findings through newsletters and media releases.

DISCUSSION

This systematic review and meta-analysis will comprehensively quantify the impacts of prenatal maternal mental health disorders on the risk on stillbirth and infant mortality. The findings will provide important information essential for practitioners and policymakers, identify research gaps in the literature and provide a foundation for future studies in this area.

Strengths and limitations

To our knowledge, this systematic review will be the first to comprehensively synthesise and quantify the impact of both severe and more common forms of prenatal maternal mental health disorders on

stillbirth and infant mortality. The other strengths of this systematic review include the use of several databases with no time restrictions, and use of independent screening and evaluation. However, the review is anticipated to have some limitations. These include heterogeneity between studies in the exposure of interest and restriction to studies in English language, which may exclude important literature and compromise generalizability.

Contributors: AA, HB and CS conceived the study and developed the search strategy. AA drafted the protocol and tested the search strategies in consultation with a librarian. RM, BF, SW and VM provided advice on the protocol. All authors critically revised the protocol for methodological and intellectual content and have read and approved the final manuscript.

Competing interests: The authors declare that they have no competing interests.

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Amendments of the protocol: If there is a need to amend this protocol, the date of each amendment and the reason for the change will be described.

REFERENCES

1. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011;377(9774):1331-40.
2. Simpson LL. Maternal medical disease: Risk of antepartum fetal death. Seminars in Perinatology 2002;26(1):42-50.
3. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1725-74.
4. Blencowe H, Cousens S, Jassir FB, et al. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2016;4(2):e98-e108.
5. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 2004;103(4):698-709.
6. Fawcett EJ, Fairbrother N, Cox ML, White IR, Fawcett JM. The Prevalence of Anxiety Disorders During Pregnancy and the Postpartum Period: A Multivariate Bayesian Meta-Analysis. J Clin Psychiatry 2019;80(4).
7. Zhong Q-Y, Gelaye B, Fricchione GL, Avillach P, Karlson EW, Williams MA. Adverse obstetric and neonatal outcomes complicated by psychosis among pregnant women in the United States. BMC pregnancy and childbirth 2018;18(1):120.
8. Ban L, Tata LJ, West J, Fiaschi L, Gibson JE. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PloS one 2012;7(8):e43462.
9. Nilsson E, Hultman CM, Cnattingius S, Olausson PO, Bjork C, Lichtenstein P. Schizophrenia and offspring's risk for adverse pregnancy outcomes and infant death. Br J Psychiatry 2008;193(4):311-5.
10. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. JAMA Psychiatry 2010;67(10):1012-24.
11. Ding XX, Wu YL, Xu SJ, et al. Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J Affect Disord 2014;159:103-10.
12. Zuckerman B, Amaro H, Bauchner H, Cabral H. Depressive symptoms during pregnancy: relationship to poor health behaviors. Am J Obstet Gynecol 1989;160(5 Pt 1):1107-11.
13. Surkan PJ, Patel SA, Rahman A. Preventing infant and child morbidity and mortality due to maternal depression. Best practice & research Clinical obstetrics & gynaecology 2016;36:156-68.
14. Khalifeh H, Brauer R, Toulmin H, Howard LM. Perinatal mental health: What every neonatologist should know. Early Hum Dev 2015;91(11):649-53.
15. Webb R, Abel K, Pickles A, Appleby L. Mortality in offspring of parents with psychotic disorders: a critical review and meta-analysis. American Journal of Psychiatry 2005;162(6):1045-56.
16. Bitew T, Hanlon C, Kebede E, Honikman S, Fekadu A. Antenatal depressive symptoms and perinatal complications: a prospective study in rural Ethiopia. BMC Psychiatry 2017;17(1):301.
17. Chen YH, Tsai SY, Lin HC. Increased mortality risk among offspring of mothers with postnatal depression: a nationwide population-based study in Taiwan. Psychol Med 2011;41(11):2287-96.
18. Goedhart G, Snijders AC, Hesselink AE, van Poppel MN, Bonsel GJ, Vrijkotte TG. Maternal depressive symptoms in relation to perinatal mortality and morbidity: results from a large multiethnic cohort study. Psychosomatic Medicine 2010;72(8):769-76.
19. Huang HC, Sung FC, Chen PC, et al. Obstetric outcomes in pregnant women with and without depression: population-based comparison. Sci Rep 2017;7(1):13937.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
21. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. http://www. ohri. ca/programs/clinical_epidemiology/oxford. asp 2001.

22. Higgins JP, Altman DG. Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions: Cochrane book series 2008:187-241.
23. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
24. Stanley TD, Doucouliagos H. Meta-regression approximations to reduce publication selection bias. Res Synth Methods 2014;5(1):60-78.
25. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. metan: fixed- and random-effects meta-analysis. Stata Journal 2008;8(1):3-28.
26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed.) 2003;327(7414):557-60.

Appendix A. databases and searching techniques

Medline (Ovid)

1. mental disorders/ or anxiety disorders/ or "bipolar and related disorders"/ or mood disorders/ or "p spectrum and other psychotic disorders"/ or substance-related disorders/
2. Depression/
3. (depression or anxiety or mental disorders or schizophrenia or psychosis).tw.
4. 1 or 2 or 3
5. Fetal Mortality/ or Child Mortality/ or Infant Mortality/ or Perinatal Mortality/
6. Infant Death/ or Fetal Death/ or Perinatal Death/
7. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
8. pregnancy outcome.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to (human and english language)

EMBASE (Ovid)

1. mood disorder/ or psychosis/ or schizophrenia spectrum disorder/
2. perinatal depression/ or depression/
3. anxiety/ or anxiety disorder/
4. (psychiatric disorder or mental disorder or mental disorders or psychosis or panic or schizophrenia or depression).tw.
5. 1 or 2 or 3 or 4
6. fetus mortality/
7. child death/
8. fetus death/ or stillbirth/
9. infant mortality/ or perinatal mortality/ or perinatal death/ or fetus death/
10. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
11. pregnancy outcome/
12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12
14. limit 13 to (human and english language)

PsycINFO (Ovid)

1. anxiety/ or panic attack/ or panic disorder/
2. affective disorders/ or anxiety disorders/ or bipolar disorder/ or chronic mental illness/ or psychosis/ or "substance related and addictive disorders"/
3. (depression or anxiety or mental disorders or schizophrenia or psychosis).tw.
4. 1 or 2 or 3
5. pregnancy outcomes/
6. Sudden Infant Death/
7. (stillbirth or fetal death or neonatal death or neonatal mortality or perinatal death or perinatal mortality or infant death or infant mortality).tw.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to (human and english language)

Scopus

Will be used to search citations and references of relevant recorders identified from the three main databases.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7 & 1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	8
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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