BMJ Open

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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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 guidelines and will be registered with the International Prospective Register of Systematic Reviews. 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 (Grading of Recommendations, Assessment, Development and Evaluations) 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.

PROSPERO registration number 159834.

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-term 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 birth weight, 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

(eg, cortisol), inflammatory response 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 the best of 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 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 terms related to maternal mental health disorders and early life mortality (stillbirth and infant mortality), tailored to each database, will be used to identify the relevant literature. The reference lists and citations of the retrieved articles will also be 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 an online supplementary 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 or relative risks 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 (AAA and HDB) based on the inclusion criteria. The full documents of the eligible abstracts will be further examined by the same authors. Finally, the 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 standardised Excel sheet. The data will also be extracted on other relevant characteristics such as maternal age, infant sex, birth weight and 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 (CCJS and VAM) 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 the outcome of interest (for cohort studies). The overall scores range from 0 to 9, with low (scores between 1 and 4), medium (scores between 5 and 7) or high quality (scores between 8 and 9) grading. The risk of bias for each study will be assessed following the GRADE

(Grading of Recommendations, Assessment, Development and Evaluations) approach.[22] Two of the authors (AAA and HDB) will perform the independent quality and risk of bias appraisals.

Funnel plots, a graphical illustration of effect estimates against their measure of precision (eg, SE), 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% 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 ($I^2 \leq 25\%$), moderate ($I^2 \leq 50\%$) 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 V.15 (StataCorp, College Station, Texas, USA).

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. 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 of 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 the best of 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 generalisability.

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