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Hypertensive disorders of pregnancy and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Hypertensive disorders of pregnancy (HDPs), that is chronic hypertension, gestational hypertension, pre-eclampsia (de novo or superimposed on chronic hypertension) and white coat hypertension, affect approximately 5%–15% of pregnancies. HDP exposure has been linked to an increased risk of autism spectrum disorder, attention deficit/hyperactivity disorder and other neurodevelopmental disorders in children. However, findings are inconsistent, and a clear consensus on the impact of HDPs on the risk of neurodevelopmental disorders is needed. Therefore, we aim to synthesise the published literature on the relationship between HDPs and the risk of neurodevelopmental disorders in the form of a systematic review and meta-analysis.

Methods and analysis We will include cohort, case–control and cross-sectional studies in which diagnosis of an HDP was reported, and neurodevelopmental disorders were the outcome of interest based on a preprepared protocol. A systematic search of PubMed, CINAHL, Embase, PsycINFO and Web of Science will be conducted in accordance with a detailed search strategy. Two authors will independently review the titles and abstracts of all studies, perform data extraction using a standardised data collection form and assess study quality using a bias classification tool. Meta-analyses will be performed to calculate overall pooled estimates using the generic inverse variance method. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Ethics and dissemination This proposed systematic review and meta-analysis is based on published data, therefore, does not require ethics approval. Findings will be presented at scientific conferences and disseminated through publication in a peer-reviewed journal.

Registration CRD42017068258.

Strengths and limitations of this study

- The proposed systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines, ensuring consistency and uniformity in reporting the full systematic review.
- The review aims to provide a clear consensus on the relationship between hypertensive disorders of pregnancy and neurodevelopmental disorders in the offspring.
- Two reviewers will screen for study eligibility and perform the quality assessment, minimising the likelihood of reviewer-based bias in the systematic review.
- A limitation of the review is that it will only include the published literature in the English language.

INTRODUCTION

Hypertensive disorders of pregnancy (HDPs) are the most common complications of pregnancy estimated to affect approximately 5%–15% of all pregnancies.[1 2] HDPs are classified into four categories, as recommended by the International Society for the Study of Hypertension in Pregnancy[3]: 'chronic hypertension', 'gestational hypertension', 'pre-eclampsia—de novo or superimposed on chronic hypertension' and 'white coat hypertension'. While HDPs are not fully understood, risk factors include advanced maternal age and elevated body mass index, both of which are increasingly common in modern society.[4] HDP create a hostile in utero environment as a result of multiple pathophysiological changes including reduced placental blood flow, maternal inflammation and oxidative stress.[5] These can potentially alter fetal developmental trajectories, which may increase the risk of long-term vascular, cognitive and psychiatric sequelae in the offspring.[4 6–8]

Neurodevelopmental disorders including autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) are a group of conditions with onset during the developmental period and may lead to impairments in personal, social, academic or occupational functioning.[9 10] Though

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these disorders have a strong genetic basis,[11 12] there is increasing evidence suggesting that environmental risk factors during prenatal development may also play a role.[11 13–18] In support of this, a population-based study conducted on a Swedish population estimated that genes and environmental exposure each contribute approximately half of the overall risk of ASD, with this 50/50 contribution remaining consistent across the study's 24-year span.[11] Furthermore, recent work demonstrated focal patches of abnormal laminar architecture and laminar disorganisation in the prefrontal and temporal cortices of children with ASD suggesting there may be alterations in brain development at prenatal stages, as cortical lamination is ongoing during the second trimester of pregnancy.[19 20] Moreover, there is some evidence for alterations in brain structural and vascular anatomy[21] and reduced cognitive functioning[22] in offspring of pregnancies complicated by pre-eclampsia pregnancies. There is therefore a need to determine the impact of HDP exposure on the risk of adverse neurodevelopmental outcomes in the children.

Early identification and intervention

There is a growing consensus that early identification and intervention are key to improving long-term neurodevelopmental outcomes.[23 24] Previously published work has indicated that early behavioural intervention if commenced before 30 months old, can lead to improvements in cognitive and adaptive behaviour among individuals with ASD.[25 26] Despite this increasing recognition for surveillance, the average age of ASD diagnosis remains at approximately 4–5 years, meaning the window for intervention has closed.[23 27 28] However, research suggests that a stable diagnosis can be made as young as 2 years, allowing earlier access to specialised services.[29] Therefore, by examining the potential impact of HDP on neurodevelopment in offspring, it can inform the need for increased paediatric surveillance of infants who have been exposed to HDP. This in turn could allow for early intervention that may aid improvement of neurodevelopmental outcome.[23 25 26 30]

Rationale for current systematic review

Evidence suggests that HDP may lead to an increased risk of ASD, ADHD as well as other neurodevelopmental disorders in children.[15 31 32] Conversely, other studies have reported no association,[13 31] highlighting the need for further study in this area. Therefore, the aim of this systematic review and meta-analysis is to summarise the available evidence examining the association between pre-eclampsia and gestational hypertension, and subsequent risk of neurodevelopmental disorders in exposed children, and if possible to identify an overall pooled estimate of association. The systematic review will be based on the following requirements:

Population

Pregnant women and their children.

Intervention/exposures

HDP.
Primary exposure: pre-eclampsia.
Secondary exposure: other HDP.

Comparison

No diagnosis of HDP.

Outcomes

Primary outcome 1: ASD.
Primary outcome 2: ADHD.
Secondary outcomes: other neurodevelopmental disorders.

METHODS AND DESIGN

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[33]

OBJECTIVES

This study aims to conduct a systematic review and meta-analysis to examine the association between HDP and neurodevelopmental disorders in the offspring.

REVIEW QUESTION

This systematic review will address the following research question:

What are the pooled estimates from existing literature examining the association between HDP and neurodevelopmental disorders in the offspring?

CRITERIA FOR CONSIDERING STUDIES FOR THE REVIEW

Inclusion criteria

- We will include cohort, case–control or cross-sectional studies in which a diagnosis of HDP was reported and neurodevelopmental disorders are the outcome of interest.
- Examining the association between HDP and neurodevelopmental disorders must be part of the main objective of the study. (This includes studies that aimed to look at other perinatal risk factors in addition to HDP.)
- Data must be from an original study, and HDP may be confirmed through medical records or doctor-diagnosed self-reporting.
- We will include studies published in English only, including all years from inception of the electronic databases until June 2017.
- Peer-reviewed literature only will be included.
- Neurodevelopmental and other behavioural or cognitive outcomes will be the focus of this review. Motor disorders have been included in the search strategy to capture studies that have included these outcomes.

Exclusion criteria

- Studies that are not in English.

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- Studies where the participants are not human.
- Case reports, case series, letters, commentaries, notes, editorials and conference abstracts.

Search strategy for identifying relevant studies

Bibliographic database searches

1. One reviewer (GMM) will conduct a systematic search of the literature in the following electronic databases: PubMed, CINAHL, Embase, PsycINFO and Web of Science. A detailed search strategy has been compiled, and these terms will be searched according to the principles of Boolean Logic (AND, OR and NOT) and using Medical Subject Headings. For example, ('Pre-eclampsia' OR 'gestational hypertension') AND ('autism spectrum disorder' OR 'attention deficit/hyperactivity disorder' OR 'neurodevelopmental disorder'). (The full search strategy is included in online supplementary file 1).
2. Searches of the electronic databases will be supplemented by hand-searching the reference lists of included studies for further potentially eligible studies.

Selection of studies for inclusion in the review

Titles and abstracts of studies retrieved from each database search will be stored and managed in EndNote reference manager. Two review authors (GMM and ASK) will independently review the titles and abstracts of all studies. Full texts will be obtained where necessary to screen for eligibility in the systematic review and meta-analysis in accordance with the predefined inclusion/exclusion criteria. Where consensus on eligibility cannot be achieved, a third review author (GWOK) will be involved in the discussion.

Data extraction and management

Using a standardised data collection form, two reviewers (GMM and GWOK) will independently extract data from the eligible studies including the author and year of publication, study design, definition of exposure and outcome used, sample size, confounders adjusted for (if any) as well as crude and adjusted estimates. Discrepancies will be resolved by a third reviewer (ASK) if necessary.

Appraisal of the quality of included studies

Quality assessment of the included studies will be conducted by two reviewers (GMM and PMK) independently and agreed on subsequently using an appropriate quality assessment tool depending on the study design. Discrepancies will be resolved by a third reviewer (ASK) if necessary. A bias classification tool described in detail elsewhere will be used.[34] In summary, this tool uses a checklist to assess common features of the six types of bias most often associated with observational studies (selection, exposure, outcome, analytic, attrition and confounding). Study bias is then classified as minimal, low, moderate, high or not reported for each of the six types of bias and an overall likelihood of bias based on the total of the six types of bias will be measured and reported. For example, selection bias will be minimised if the sample was taken from a 'consecutive unselected population', while conversely a study with high selection bias will arise if sample selection is ambiguous and the sample is not likely representative.

Data synthesis including assessment of heterogeneity

Where the data allow, meta-analyses will be performed to calculate overall pooled estimates of the relationship between combined HDP, pre-eclampsia and gestational hypertension, and different disorders of neurodevelopment. Both crude and adjusted results will be displayed where possible using the generic inverse variance method. Adjustment will be based on the definition outlined in each identified study and a hierarchy of adjustment created depending on the factors that are adjusted for. Studies that report similar adjustments will be analysed separately in crude and adjusted models to assess potential confounding among studies that reported adjusted estimates.

A fixed-effects model will be used where heterogeneity is low (I^2 value of less than 50%), and a random-effects model where heterogeneity is high (I^2 value of 50% or more) according to the Cochrane Handbook criteria.[35]

We will also perform the following subgroup/sensitivity analyses where the data allow, using RevMan 5.3:

1. according to study design (cohort vs case–control vs cross-sectional)
2. according to studies that report estimates for the association between pre-eclampsia and gestational hypertension and each neurodevelopmental disorder
3. according to location (eg, Europe vs USA)
4. according to income level of country (low/middle/high)
5. according to study quality (minimal/low vs moderate/high)
6. according to measurement of exposure and outcome data (self-reported vs medical records based on varying clinical coding systems).

Publication bias will be assessed using a funnel plot provided at least 10 or more studies are included in the meta-analysis. The trim and fill method will also be used to identify and correct for funnel plot asymmetry arising from publication bias.[36] Where any other subgroup/sensitivity analyses are identified in the process of the meta-analysis, such as analyses to explore potential high heterogeneity or publication bias, these will be clearly labelled as post hoc analyses.

Presenting and reporting the results

A flow diagram (as outlined in the PRISMA statement[33]) will be included to outline the study selection process step by step, and a rationale provided for excluded studies. The characteristics and quality assessment of the included studies will be presented in tables. Pooled estimates will be presented using forest plots. Where a study is eligible for inclusion in the systematic review but does not provide adequate data to include in a meta-analysis,

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we will contact the corresponding authors in an attempt to obtain raw data where appropriate. If raw data cannot be obtained, the findings will be included individually in a separate table.

CONCLUSION

This systematic review and meta-analysis will summarise existing literature examining the association between HDP and different disorders of neurodevelopment based on a preprepared protocol. By identifying the possible contributors to adverse neurodevelopmental outcomes, it may lead to early identification and intervention. Therefore, by examining potential aetiologies of neurodevelopmental disorders, it may inform the need for greater paediatric surveillance of HDP-exposed infants to allow early intervention, which may aid improvement of neurodevelopmental outcome.[23 25 26 30]

Potential limitations

It is anticipated that publication bias may pose as a limitation for this review. Studies that show an effect have an increased likelihood of being published as well as being published in English. Due to limited resources, the systematic review search will be confined to studies published in the English language only, potentially resulting in publication bias as well as relevant indexed studies being overlooked. If possible, a funnel plot will be used to assess the presence of publication bias.

Furthermore, the presence of confounding is a major concern in observational studies. Potential confounders may include infant sex, family's socioeconomic status, ethnicity, maternal age, parity, maternal smoking and alcohol status during pregnancy, maternal use of antidepressants (during pregnancy or during the preconception period) and maternal mental illness, while preterm delivery and small for gestational age could potentially play a confounding or mediating role. As mentioned above, our meta-analyses will display both crude and adjusted results where possible using the generic inverse variance method, basing adjustment on the definition outlined in each identified study.

Ethics and dissemination

Given that this is a protocol for a systematic review and based on published data, there is no requirement for ethics approval. It is anticipated that dissemination of results will take place at conferences and through publication in a peer-reviewed journal.

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Contributors GMM and ASK conceived and designed the protocol, and GMM drafted the protocol manuscript. GMM and ASK participated in the development of the search strategy. GMM and GWOK planned the data extraction. GMM and PMK planned quality appraisal of included studies. GWOK, LCK, PMK, TGD and ASK critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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