Obstetrics & Gynaecology Publications

Obstetrics & Gynaecology Department

10-1-2022

# Highlighting the Mechanistic Relationship Between Perinatal Depression and Preeclampsia: A Scoping Review

Mei Yuan
*Schulich School of Medicine & Dentistry*

Samantha Bedell
*Schulich School of Medicine & Dentistry*

Barbra De Vrijer
*Schulich School of Medicine & Dentistry*

Genevieve Eastabrook
*Schulich School of Medicine & Dentistry*, genevieve.eastabrook@lhsc.on.ca

Jefferson C. Frisbee
*Schulich School of Medicine & Dentistry*

*See next page for additional authors*

## Authors

Mei Yuan, Samantha Bedell, Barbra De Vrijer, Genevieve Eastabrook, Jefferson C. Frisbee, and Stephanie J. Frisbee

*Mary Ann Liebert, Inc.* publishers

Open camera or QR reader and scan code to access this article and other resources online.

## REVIEW ARTICLE                                    Open Access

# Highlighting the Mechanistic Relationship Between Perinatal Depression and Preeclampsia: A Scoping Review

Mei Yuan,[1] Samantha Bedell,[2] Barbra de Vrijer,[2,3] Genevieve Eastabrook,[2,3] Jefferson C. Frisbee,[4] and Stephanie J. Frisbee[1,3,5,*]

## Abstract

**Background:** Although there is scientific literature supporting an association between depression and pre-eclampsia (PE), little is known about the underlying mechanistic pathways that may explain these observed associations. Thus, this study aimed to outline the relationship between depression and PE, and to highlight the underlying cardiovascular and metabolic risk factors that are common to both.

**Methods:** A scoping review of the literature was conducted in Medline, Scopus, and Web of Science.

**Results:** From 706 articles initially identified, 23 articles met the inclusion criteria and were included in this review. Although some studies reported a positive association between PE and postpartum depressive symptoms, challenges comparing different methodologies, measurement instruments and when measurements were administered, and patient populations do not permit a decisive conclusion. In addition, very few studies addressed potential underlying mechanisms that may be contributing to observed associations; thus, a secondary search was conducted to identify cardiovascular and metabolic risk factors that are common to both depression and PE.

**Conclusion:** The cardiovascular and metabolic risk factors (*i.e.,* increased inflammation and oxidative stress and decreased vascular and endothelial function) common to both depression and PE suggest that these factors may contribute as underlying mechanisms in both conditions. These similarities underscore the importance to better understand these mechanisms so preventative and therapeutic strategies could be developed to improve maternal health.

**Keywords:** pregnancy; antenatal depression; depressive symptoms; preeclampsia; gestational hypertension; postpartum depression; cardiovascular disease risk factors

[1]Department of Pathology and Laboratory Medicine, [2]Maternal-Fetal Medicine, Department of Obstetrics and Gynaecology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Canada.
[3]Lawson Health Research Institute, London, Canada.
[4]Department of Medical Biophysics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Canada.
[5]Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Canada.

*Address correspondence to: Stephanie J. Frisbee, PhD, MSc, Department of Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, 1151 Richmond Street, Dental Sciences Building, Room 4041, London N6A 5C1, Canada, E-mail: sfrisbee@uwo.ca

## Background

Hypertensive disorders of pregnancy are a broad spectrum of conditions ranging from chronic hypertension to preeclampsia (PE) and eclampsia. In 2018, ~7% of all pregnancies in Canada were complicated by hypertensive disorders of pregnancy.[1] PE is defined as having hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), certain end-organ dysfunction, and with or without new-onset proteinuria.[1,2] PE can lead to health consequences such as long-term end-organ dysfunction, fetal developmental issues, and even death for both mother and fetus.[2,3] Known risk factors for PE include age, nulliparity, chronic hypertension, body mass index (BMI) >30 kg/m$^2$, and preexisting diabetes.[4] Of concern is evidence from epidemiologic studies demonstrating the increased prevalence of these risk factors in women of childbearing age.[5,6] In Ontario, between 2012 and 2016, 17.8% of mothers with live singleton or twin births had a prepregnancy BMI >30 kg/m$^2$, and 1.1% had established chronic hypertension.[7] Average maternal age has also steadily risen since the mid-1960s, with the average maternal age at first pregnancy now at 30.8 years.[8] Additional factors presenting challenges to pregnant women are mental health concerns, particularly depression and depressive symptoms. In Canada, ~5% of women have major depressive disorder,[9] in Ontario, 7.7% of mothers were affected with depression during pregnancy,[10] 8.6% of women experience postpartum depressive symptoms,[11] and 54.2% of women who experienced postpartum depression had depression previously.[10,12]

Increasing attention is being paid to the interrelationships between preexisting mental health concerns, particularly depression, obesity, and PE. For example, one study reported that, in pregnant women, a one unit increase in prepregnancy BMI was associated with ~3% higher odds of antenatal depression.[13] These findings suggest an interplay between physical and mental health, or risk factors that are similar for both entities.

Despite known associations between depression and PE, much less is understood about the possible mechanistic pathways connecting these two conditions. Thus, the first objective for this study was to conduct a scoping review to summarize research findings regarding the association between depression and PE. The secondary objective was to extract information from previously reported studies, particularly related to underlying cardiovascular and metabolic risk factors, and integrate this information with the goal to provide evidence for and insights into the possible mechanistic pathways connecting depression and PE.

## Methods
### Identifying the research question

This scoping review was conducted using the methodological framework described by Arksey and O'Malley.[14] The primary research question for this scoping review was, "what is the current evidence for an association between depression and preeclampsia"? As most of the screening tools used to assess depression during pregnancy within research are solely to identify those in need of further clinical assessment, the distinction between depressive symptoms and clinical diagnosis of depression is not often made, thus for this scoping review, the term "depression" includes the entire spectrum of the disease. The secondary research question for this scoping review was, "what information has been reported that provides insight into pathophysiologic mechanisms that might link depression and preeclampsia"?

### Identifying relevant studies

This scoping review identified, retrieved, and evaluated information from peer-reviewed scientific articles that examined the association between depression and PE in pregnant women. The focus was on studies published between 2000 and 2020, as it reflected the most recently published literature. Two authors performed the search using a combination of search terms related to our target group, depression, and PE (Table 1) within the following international databases: Medline (2000–April 2020), Scopus (2000–2019), and Web of Science (2000–2020). The search strategies were limited to scientific journal articles and English language only.

**Table 1. Keywords and Search Terms Used in the Database Searches**

| Target group or population | Issue | Outcomes |
|---|---|---|
| Pregnant Pregnancy | Depression Depressive symptoms Major depressive symptoms Prenatal depression Antenatal depression Postpartum depression | PE |

PE, preeclampsia.

### Selecting the literature
**Inclusion and exclusion criteria.**   Inclusion criteria for studies included in this scoping review were as follows: (1) an examination of the associations between depression and PE during pregnancy and/or postpartum, and (2) measurement of maternal depression and PE during pregnancy and/or postpartum. Studies were excluded if: (1) depression was pooled with other variables, such as anxiety, stress, and mood disorder, or the PE measurement was pooled with perinatal outcomes, and (2) if the study did not separately assess depression without antidepressant medication. The exclusion of these articles allowed for a more focused examination of the relationships between depression and PE, as covariates such as antidepressant medication have been reported to affect either depression or PE. The specific inclusion and exclusion criteria are given in Table 2. As we included different types of studies in this scoping review (primary studies and review studies), and there is not a single approach to compare the quality of these different types of studies, we did not include a formal assessment of the methodological quality of the included studies. However, we include in the summary table multiple characteristics of the study, including sample size and design, for readers to review and consider.

Duplicate articles were identified by the search tool and removed from the database before screening. A two-step process was performed by two authors (M.Y. and S.F.) (Fig. 1). During the first stage, the titles and abstracts of the identified articles were screened according to the exclusion and inclusion criteria described previously. Uncertainty during the initial title and abstract screening was resolved by consulting the full-text articles.

**Abstracting information and summarizing data from included studies.**   Studies that met the inclusion criteria were screened further as full articles. Full-text screening was assessed for final inclusion into the study, with the selected full-text articles passing an additional bibliographic reference list check to identify any additional eligible publications. The articles reviewed were categorized and summarized depending upon whether the study assessed the outcomes of interest during prenatal period (before the birth of the newborn) or postpartum period (after delivery of the newborn). Information such as the author, year of publication, study design, study population, outcomes, relevant findings, and information about underlying cardiovascular or metabolic risk factors examined was also abstracted.

### Supplemental literature search
To better interpret and supplement the information abstracted from studies included in this scoping review related to the secondary research question (pathophysiologic mechanisms that might link depression and PE), a supplemental literature search was conducted. This general search, conducted in PubMed, identified research studies with information that could better explain information regarding the underlying mechanisms of depression and PE obtained from studies included in this scoping review.

## Results
Twenty-three articles were included in this scoping review. Nine studies were conducted in North America, six in Europe, five in Asia, two in South America, and one in Africa. Four meta-analyses were included as they fit the inclusion criteria in addressing the research question, despite having a few studies within the meta-analyses that overlapped with those already included within the review. Twelve studies were published in the most recent 5 years.

### Associations between prenatal depression and PE during pregnancy
Of all 23 articles reviewed, 13 explored the associations between prenatal depression and PE during pregnancy (Table 3). Some studies reported a significant positive association between the two factors,[15–20] but other studies did not observe such associations or reported associations that were not statistically significant.[21–23] In a prospective case–control study carried out in Iran, Kharaghani et al observed that women with mild depression and severe to moderate depression had a 1.81-fold and 2.52-fold increased risk of developing PE, respectively.[17] Conversely, Ghaffar et al

**Table 2. Inclusion and Exclusion Search Terms in All Three Databases**

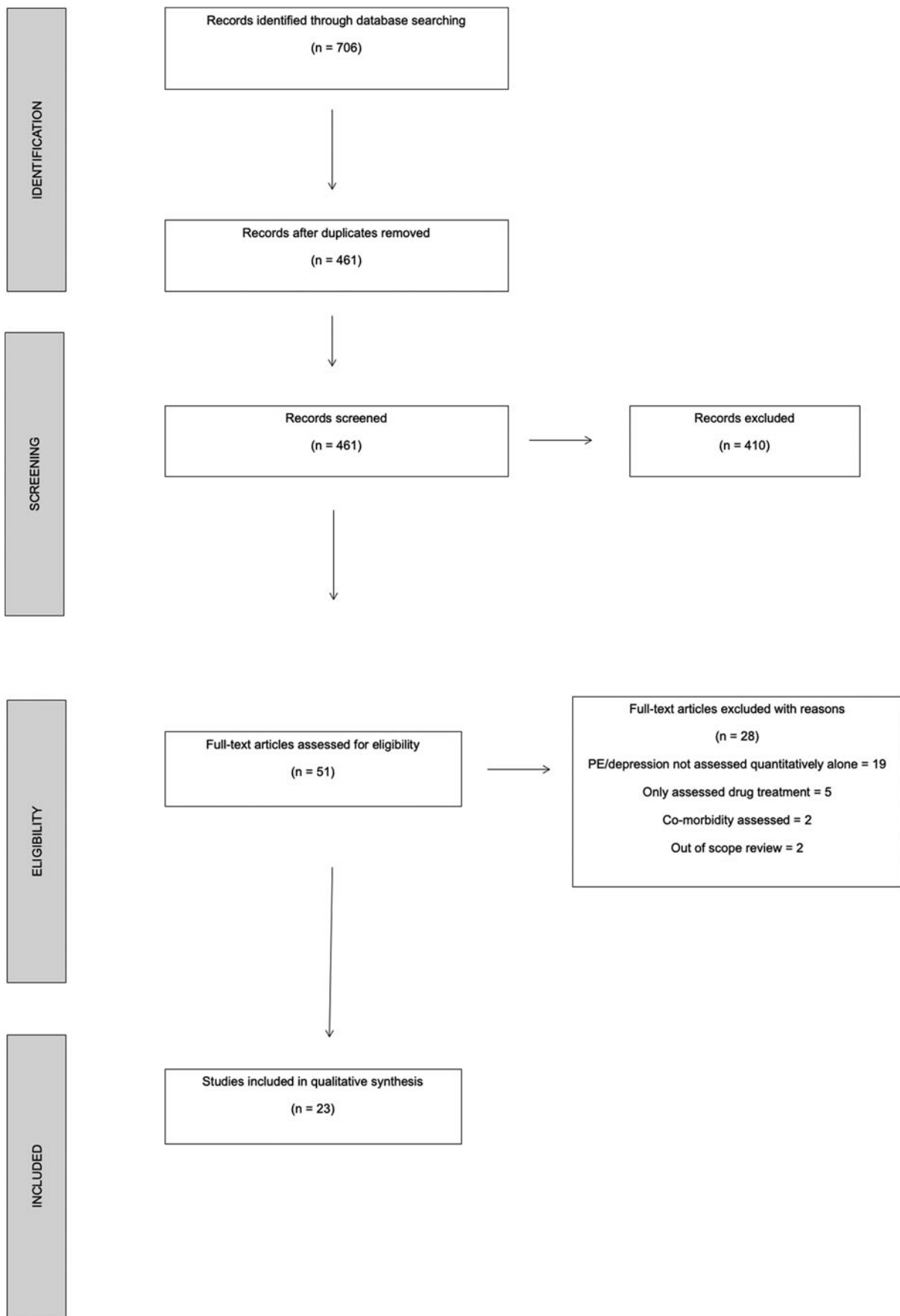| Inclusion | Exclusion |
|---|---|
| Journal articles | Neonatal outcomes |
| English language | Comorbidities (preexisting disease of liver, kidney, autoimmune disease, *etc.*) |
| Human population | Drug |
| Direct measurement of depressive symptoms/PE | Pharmaceutical |
| | Therapy |
| | Treatment |

**FIG. 1.** PRISMA-Sr search strategy. This flowchart displays the search process from identification of relevant literature to final inclusion of full test articles.

**Table 3. Summary and Synthesis of Primary Studies Examining the Relationship Between Prenatal Depressive Symptoms and Preeclampsia**

| First author and year | Country | Study design | Study population and sample size | Measurements/ assessment tools | Outcome | Relevant findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|---|
| Bansil et al (2010)[16] | United States | Retrospective cross-sectional | In-hospital delivery visits from 1998 to 2005 nationwide inpatient sample of women aged from 15 to 44; $n=32,156,438$ | ICD-9 codes for concurrent diagnosis of depression and pregnancy complications, including PE | PE | 1.57 risk of PE (OR, 95% CI, 1.52–1.62) in women with depression; rate of depression increased during the 7-year study period (2.73/1,000 to 14.12/1,000 deliveries in 2005) | Not examined in this study |
| Ghaffar et al (2016)[21] | Pakistan | Prospective cross-sectional | Pregnant women 16–40 years old at >12 weeks' gestation, presenting with obstetric risk to a tertiary hospital; $n=230$ | EPDS administered at mid-pregnancy; participants classified as depressed or not depressed (score >11) | Hypertension, PE, eclampsia, and other pregnancy complications | 60% of participants were classified as depressed. Significant statistical associations between depression and hypertension, but no statistically significant associations reported between depression and PE, eclampsia, or other pregnancy complications | Hypertension associated with depression |
| Kharaghani et al (2012)[17,a] | Iran | Prospective case–control | All new singleton admission to the hospitals around 35.7 weeks, $n=156$ with PE, 156 pregnant with healthy pregnancy | PHQ-9 at enrolment (mean gestational age was 35.6 weeks) | PE | Moderate-to-severe depression observed in 31.2% of the PE group (24.8% in control). Statistically significant associations observed in trend test for severity of depressive symptoms and PE (statistically significant mild depression had 1.81 (OR, 95% CI, 1.05–3.14)-fold increase risk of PE; severe to moderate depression had a 2.52 (1.05–6.02)-fold increase) | Associations between depression and PE remained statistically significant after adjusting for prepregnancy BMI, but magnitude of statistical significance of BMI itself was not reported |
| Kim et al (2013)[20,a] | United States | Retrospective cohort | Analyzed data from black, non-Hispanic pregnant women presenting for initial prenatal visit, with singleton birth past 20 weeks gestational age; $n=261$ | EPDS at initial pregnant visit; mean gestational age for EPDS screening was 17.2 weeks | PE, IUGR, PTB | An EPDS score[3] 10 was statistically significantly risk factor for PE (OR=2.95, 95% CI, 1.26–6.89), PTB, and IUGR; 9.6% of the women had PE | Not examined in this study |

854

(continued)

**Table 3. (Continued)**

| First author and year | Country | Study design | Study population and sample size | Measurements/assessment tools | Outcome | Relevant findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|---|
| Kurki et al (2000)[15,a] | Finland | Prospective cross-sectional | Pregnant women enrolled at first prenatal visit between 8 and 17 weeks' gestation; specific exclusion for elevated risk of PE, essential hypertension, GDM, and twins; $n=623$ | BDI conducted at median 12 weeks' of gestation | PE | Depression associated with 2.5-fold increased for PE (95% CI, 1.2–5.3) | Not examined in this study |
| Palmsten et al (2012)[22] | Canada | Prospective cohort | Live birth pregnancies with continuous health care enrolment until 2 months after delivery; at least one inpatient or outpatient code for depression during year before LMP; $n=306,831$ pregnancies from 224,827 women | ICD-9 codes for PE and depression diagnosis | PE | No statistically significant results reported as the risk of PE was similar in women without depression and women with depression, but no antidepressant dispensing (2.3% vs. 2.4%) | Not examined in this study |
| Qiu et al (2007)[18,a] | Peru | Prospective case–control | Cases: women with PE diagnosis at 20 weeks' gestation; controls: women with uncomplicated pregnancies; $n=339$ case and 337 control | PHQ-9 during pregnancy | PE | Moderate depression (score 10–14) during pregnancy had 2.6-fold increase risk of PE (OR=2.6; 95% CI, 1.4–4.6); moderate-to-severe depression (score, 15–19) was associated with 3.2-fold increase risk (OR=95% CI, 1.1–9.6) of PE after adjusting for confounders | Associations between depression and PE remained statistically significant after adjusting for prepregnancy BMI, but magnitude of statistical significance of BMI itself was not reported |

(continued)

**Table 3. (Continued)**

| First author and year | Country | Study design | Study population and sample size | Measurements/ assessment tools | Outcome | Relevant findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|---|
| Qiu et al (2009)[19] | United States | Retrospective cohort | Women who initiated prenatal care before 20 weeks gestation, older than 18 years old, delivered at the required hospital; n=2,601 | Depression and PE diagnosis based on medical records (could be ICD or just self-report for depression); data analyzed women enrolled between 1996 and 2004 | PE | Disorders diagnosed during the first 20 weeks of pregnancy were more strongly related with PE risk (RR=3.64; 95% CI, 1.13–11.86); women classified as having any mood or anxiety disorder had 2.12-fold increased risk of PE (RR=2.12, (1.02–4.45); women with isolated mood disorder had 2.72-fold increased PE risk compared to women without psychiatric disorders (95% CI, 1.29–5.74. | Prepregnancy BMI, family history of hypertension, age, and diabetes were evaluated to see if it modified the effect of maternal mood disorders and PE risk, but no significant modifications were observed |
| Thombre et al (2015)[34] | United States | Prospective case–control | Pregnancy women over age of 15, singleton pregnancy with no known congenital or chromosomal abnormalities or pregnancy diabetes between 16 and 27 weeks of gestation; n=1,371 | Depression and anxiety symptoms: history taken at four time points; For depression within the past week, CES-D (score of 16 and greater is depressed) | PE | Prepregnancy history of depression symptoms was associated with presence of a hypertensive disorder during pregnancy (OR=1.8; 95% CI, 1.1–3.2) à driven by women with chronic hypertension | Associations between depression and PE remained statistically significant after adjusting for prepregnancy BMI and smoking, but magnitude of statistical significance of BMI and smoking was not reported |
| Vollebregt et al (2008)[23,a] | The Netherlands | Prospective cohort | Nulliparous women with singleton pregnancy who attendee antenatal care for first check-up and completed the questionnaire before 24 weeks and delivered after 24 weeks; n=3,679 | Psychosocial stress: work stress, depression (Dutch CES-D), anxiety (Dutch STAI), and pregnancy-related anxiety (revised version of Pregnancy-Related Anxiety Questionnaire | PE | No association observed between anxiety, depression, or pregnancy related anxiety and PE and GH after adjusting for medical and socioeconomic covariates | Associations between depression and PE remained statistically significant after adjusting for prepregnancy BMI, but magnitude of statistical significance of BMI itself was not reported |

*Synthesis and summary of table* | | | 10 of the 23 studies that met the inclusion criteria for this review. Seven of the 10 studies reported statistically significant associations between prenatal depressive symptoms and PE (PE)

aStudies included in the meta-analyses are given in Table 4.

BDI, Beck Depression Inventory; BMI, body mass index; CES-D, Center for Epidemiological Studies- Depression; CI, confidence interval; EPDS, Edinburgh Postpartum Depression Scale; GDM, gestational diabetes mellitus; GH, gestational hypertension; ICD-9, International Classification of Diseases, 9th Revision; IUGR, Intrauterine growth restriction; LMP, last menstrual period; OR, odds ratio; PHQ-9, Patient Health Questionnaire-9; PTB, pre-term birth; RR, relative risk.

observed no significant association in hospitalized women between depression and PE.[21] Vollebregt et al also reported no significant associations between depression and PE even after adjusting for medical and socioenvironmental factors.[23]

Pooled analyses from two meta-analyses, Hu et al (pooled odds ratio [OR] = 1.48; 95% confidence interval [CI], 1.04–2.01) and Zhang et al (pooled OR = 1.5; 95% CI, 1.10–20.5) reported statistically significant positive associations between prenatal depressive symptoms and PE.[24,25] Conversely, Grigoriadis et al did not observe any statistically significant associations between exposure to antenatal depressive symptoms and an increased risk of PE (OR = 1.35, 95% CI, 0.95–1.92).[12] Summaries and details of these three meta-analyses are given in Table 4.

### Associations between PE and postpartum depression

Ten of the 23 articles included in this scoping review investigated associations between diagnosis of PE and development of postpartum depression (Table 5). Seven studies reported significant associations between increased prevalence of postpartum depression with the diagnosis of PE.[26–32] Auger et al observed that women with PE had a higher incidence of hospitalization for depression 28 years after indexed delivery and that late-onset PE was more consistently associated with hospitalization for depression within 1–4 years after pregnancy.[30] Similarly, Bergink et al reported an increased incidence risk ratio of 2.85 (95% CI, 1.84–4.42) for unipolar depression within 0–3 months postpartum in women who developed PE.[31]

Caropreso et al was the only meta-analysis that explored the association between PE and postpartum depression in our search. The analysis reported the standard mean difference between groups of women with and without PE as 1.04 (95% CI, 0.22–1.86), which suggested high severity of depressive symptoms in women with a history of PE.[33] Study details of this meta-analysis are given in Table 6.

### Examination of common underlying cardiovascular and metabolic risk factors

The majority of the articles included in this scoping review accounted for factors associated with cardiovascular risk, such as prepregnancy BMI, smoking, preexisting hypertension, and diabetes. In the studies investigating associations between prenatal depression and PE, the associations observed between depression and PE remained after adjusting for these cardiovascular risk covariates.[18,19,23,34] In studies assessing the association between PE and postpartum depression, three of the nine studies adjusted for the confounding variable of prepregnancy BMI. As given in Table 5, all three articles, Auger et al, Mommersteeg et al, and Chen et al, reported that positive associations between PE and postpartum depression remained significant after adjustment for prepregnancy BMI.[26,30,35]

### Integration of information from supplemental literature search

Although all included studies were examined for common underlying cardiovascular and metabolic risk factors, it is important to note that none of the studies reported the magnitude of an independent association between the covariates and the association between depression and PE, or more advanced analyses such as stratification or mediation analysis that might provide insight into the characteristics underlying the observed association between PE and depression. Similarly, none of the studies specifically assessed potential common cardiovascular and metabolic risk factors such as arterial stiffness, endothelial dysfunction, or obesity between depressive symptoms and PE despite previous studies suggesting that these factors are associated with both PE and depression individually.[36–39] To provide better insight into possible pathophysiologic mechanisms that might link depression and PE, integration of the results from this scoping review and information from a supplemental scoping review focused on BMI, vascular stiffness, endothelial dysfunction, inflammation, and oxidative stress are now presented.

**Body mass index.** A high prepregnancy BMI is associated with an increased risk of antenatal depression.[40] This is unsurprising as obesity and depression outside of pregnancy are often linked and are thought to share similar biological mechanisms.[41] In addition, studies have shown that an elevated BMI increases the risk for developing PE[42,43]; although obesity alone is not a direct indicator of cardiometabolic health and recent studies have begun to consider the differences between "healthy" obesity and obesity with associated metabolic abnormalities.[44]

**Arterial stiffness.** Arterial stiffness is a good indicator of cardiovascular health and common measurements of arterial stiffness include augmentation index, which

**Table 4. Summary and Synthesis of Meta-Analyses Examining the Relationship Between Prenatal Depressive Symptoms Preeclampsia**

| First author and year | Country | Aim | Studies included within our search | Outcome | Statistical findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|
| Grigoriadis et al (2013)[12] | Canada | Whether maternal depression during pregnancy is associated with perinatal and infant outcomes | Kurki et al,[15] Vollebregt et al[23] | PE, perinatal outcomes, infant outcomes (searched Medline, PsycInfo, CINAHL, Embase, Scopus); n=30 | Association between exposure to maternal depression and PE was not statistically significant from pooled OR of 4 studies (1.35, 95% CI, 0.95–1.92) | Not examined in this study |
| Hu et al (2015)[24] | United States | Whether antenatal depression is a risk factor for PE or operative deliveries | Kharaghani et al,[17] Kim et al,[20] Kurki et al,[15] Qiu et al,[18] Vollebregt et al[23] | PE, operative deliveries (searched through PubMed, SCI/SSCI, Proquest PsycArticles, CINAHL); n=12 | Pooled OR of 1.63 times (95% CI, 1.32–2.02) increased risk for PE in patients with antenatal depressive symptoms (after adjusting for prepregnancy BMI, (OR=1.48, 95% CI, 1.04–2.10) | Associations between depression and PE remained statistically significant after adjusting for prepregnancy BMI, but magnitude of statistical significance of BMI itself was not reported |
| Zhang et al (2013)[25] | China | Whether mental stress affects gestational hypertension or PE | Kharaghani et al,[17] Kurki et al,[15] Qiu et al,[18] Vollebregt et al[23] | PE, gestational hypertension (PubMed, Cochrane, Chinese medical datasets); n=13 | 5 cohort studies, 8 case–control, pooled effect of the 12 studies suggested that mental stress was associated with an increased risk of PE (OR=1.49; 95% CI, 1.27–1.74, p<0.001); depression alone was observed to have statistically significant associations with PE (OR=1.5, 95% CI, 1.10–2.05) and no heterogeneity. Overall, the effect size in PE was larger than GH | Not examined in this study |

*Synthesis and summary of the table*

*3 of the 23 studies met the inclusion criteria for this review. Two of the three meta-analyses reported statistically significant associations between prenatal depression and PE*

**Table 5. Summary and Synthesis of Primary Studies Examining the Relationship Between Preeclampsia and Postpartum Depressive Symptoms**

| First author and year | Country | Study design | Study population and sample size | Measurement/assessment tools | Outcome | Relevant findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|---|
| Auger et al (2021)[30] | Canada | Longitudinal cohort | Women at 20+ weeks' gestation; diagnosed PE; followed for 28 years; n = 1,210,963 | ICD-9 and ICD 10 classification of PE | Incidence of depression hospitalization per 1,000 person-years (calculated using cumulative incidence function) as proxy for severe depression | In adjusted models, late-onset PE was statistically significant associated with increased risk of depression hospitalization later in life. Associations were present for 28 cumulative years, 1–4 years, 4–14 years, and ≥15 years after pregnancy | Associations between PE and depression remained statistically significant after adjusting for obesity, GDM, and diabetes but magnitudes of statistical significance was not reported |
| Bergink et al (2015)[31,a] | Denmark | Retrospective cohort | Singleton and primiparous women born in Denmark, pregnant between 1995 and 2011; n = 400,717 | Danish National Patient/Hospital Register, ICD-10 diagnosis of PE | Depression (ICD-10), based on first contact with Danish Psychiatric Central Research Register after delivery | All pregnant women were at increased risk of experiencing first-onset psychiatric episodes 0–3 months postpartum, with a considerable increased risk for women with PE | Associations between PE and depression remained statistically significant after adjusting for gestational diabetes mellitus was measured but magnitude of statistical significance was not reported |
| Chen et al (2019)[26] | China | Retrospective cross-sectional | Women aged 20–40 years old, selected from specialty postpartum clinic at 6-week visit, n = 180, 90 with PE, and 90 randomly selected non-PE controls | EPDS (score ≥10 for possible depression) at 6 weeks postpartum | Depression | Women with PE had 2.75-fold increase odds of PPD (95% CI, 1.056–7.18); severe PE diagnosis associated with 4.5-fold increase odds of PPD (95% CI, 1.94–17.255) | Associations between PE and depression remained statistically significant after adjusting for predelivery BMI, but magnitude of statistical significance of BMI itself was not reported |
| Gaugler-Senden et al (2012)[81,a] | The Netherlands | Retrospective cohort | Women diagnosed with severe PE before 24 weeks' gestation and all women with severe PE at 24–32 weeks' gestation admitted and delivered before 34 weeks; n = 104 severe PE and 78 control participants (with spontaneous preterm delivery, matched for age, parity, gestational age at delivery, ethnicity, and year of delivery) | Zung Depression Scale, Impact of Event scale, and Social Readjustment Rating scale | Women with severe PE between 1999 and 2004 were identified and asked to complete surveys in 2008. 79% response rate for PE group and 58% for control group | No observed difference in current and recalled postpartum depression scores in women with severe PE and controls with preterm delivery up to 7 years; women with induced PE observed to have higher posttraumatic score | Not examined in this study |
| Hoedjes et al (2011)[32] | The Netherlands | Prospective cohort | Participants drawn from women enrolled in the Pro-Active study; gave birth between February 2007 and June 2009, over the age of 18, had PE, and understood Dutch; n = 174 | EPDS at 6, 12, and 26 weeks postpartum, cutoff score of 10 for possible depression | Depression | Women with severe PE (ACOG criteria) group were more likely to report depressive symptoms postpartum, anytime up to 26 weeks compared with women with mild PE (44% vs. 23%); perinatal death and NICU admission were reported to be contributing factors | Not examined in this study |

(continued)

859

**Table 5. (Continued)**

| First author and year | Country | Study design | Study population and sample size | Measurement/ assessment tools | Outcome | Relevant findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|---|
| Mbarak et al (2019)[27] | Tanzania | Prospective cross-sectional | Postpartum women diagnosed with PE or eclampsia (as abstracted from discharge notes) delivered and attended postnatal clinic at MNH, enrolled before 4 weeks postpartum; n=386 | EPDS at 2–6 weeks postpartum, score >13 considered as depression | Depression | Younger women diagnosed with PE or eclampsia was more likely to suffer from PPD (AOR=10.13; 95% CI, 1.99–52.02); only 10.5% of women with mild PE had PPD, compared with 25.3% and 31.7% of women with severe PE and eclampsia, respectively | Not examined in this study |
| Mommersteeg et al (2016)[35,a] | The Netherlands | Longitudinal cohort | 4 years follow-up of women enrolled in the PREVFEM study (gave birth from 1991 to 2007, participants classified as early-onset PE or no PE based on ISSHP criteria; invited to complete mailed-in surveys in 2013; n=265 in PE group, 268 in age-matched non-PE control group | Depression: PHQ-9 (PHQ-9 score ≥5 indicating mild to severe depressive symptoms), anxiety: GAD-7, fatigue: fatigue assessment scale | Depression | PE group reported significantly more depressive symptoms after adjusting for covariates (B=0.70; 95% CI, 0.09–1.32; p=0.026) | Associations between PE and depression remained statistically significant after adjusting for BMI, but magnitude of statistical significance of BMI itself was not reported |
| Strapasson et al (2018)[28] | Brazil | Prospective cross-sectional | Convenience sampling of women who had recently delivered, HDP group had to be diagnosed with HDP after 20 weeks, age older than 18 years; n=168 (42 diagnosed with HDP, 126 normotensive) | EPDS (score ≥12 considered depressed) within 12 hours postpartum and medical charts for pregnancy outcomes and HDP diagnosis | Depression | All HDP (severe PE, superimposed PE, eclampsia) were significantly associated with PPD. Probability of postpartum depression correlated with the diagnosis of HDP was significant | Not examined in this study |
| Youn et al (2017)[29,a] | South Korea | Retrospective cross-sectional | Data extracted from Korean national health insurance system from September 2016 to January 2017 on women who gave birth between January 1, 2010 and December 31, 2012, only included the first pregnancy; n=1,269,130 | Depression included depression before pregnancy and postpartum (up to 1 year). Classified into previous history of depression (up to 1 year before birth) and depression during the postpartum period (first year after delivery) based on ICD-10 code for depression; presence of PE determined based medical records | Depression included depression before pregnancy and postpartum (up to 1 year) | PE increased risk of PPD (OR=1.12; 95% CI, 1.03–1.22). Previous history of depression had a higher risk for PPD (OR=16.72; 95% CI, 16.05–17.41); women who delivered preterm or had placental abruption were more likely to develop PPD | Not examined in this study |

*Summary and synthesis* — *9 out of the 23 studies met the inclusion criteria for this review. Eight of the nine studies reported statistically significant associations between PE (PE) and postpartum depressive symptoms.*

**Table 6. Summary and Synthesis of Meta-Analysis Examining the Relationship Between Preeclampsia and Postpartum Depressive Symptoms**

| First author and year | Country | Aim | Studies included within our search | Study design | Outcome | Statistical findings | Examination of potential underlying factors |
|---|---|---|---|---|---|---|---|
| Caropreso et al (2020)[33] | Canada | Whether PE is a risk factor for postpartum depression and psychosis | Bergink et al,[31] Gaugler-Senden et al (2012),[81] Mommersteeg et al,[35] Youn et al[29] | Meta-analysis of 8 of 13 studies reviewed (searched through PubMed, PsycInfo, Scopus, Embase), appraised using Newcastle–Ottawa scale | Depression and psychosis | All 8 studies observed association between PE and postpartum depression or depression outside the perinatal period. Postpartum: standard mean difference of depressive symptom severity between women with and without history of PE was 1.04 (95% CI, 0.22–1.86; $p = 0.01$) | Some studies assessed BMI and GDM but the review itself did not report individual magnitudes of effect on these variables in associations with PE and PPD |

This table includes 1 of the 23 studies that met the inclusion criteria for this review and indicated high severity of postpartum depressive symptoms in women with a history of PE.

represents arterial adaptability, and pulse-wave velocity. In the nonpregnant literature, depression has been associated with a higher augmentation index and pulse wave velocity measurements,[37,45–47] suggesting that individuals with depression have increased arterial stiffness that may contribute to increased cardiovascular risk. Similarly, multiple studies have reported that individuals with a current and/or previous history of PE have significantly higher pulse wave velocity and augmentation indices compared with those who had healthy, uncomplicated pregnancies.[46,48–56]

*Endothelial dysfunction.* Impaired measurements of flow-mediated dilation, an ultrasound-based imaging assessment of dilation in the brachial artery that is used to quantify the health or dysfunction of the endothelium, have been associated with depression in the nonpregnant population.[57,58] Prenatal measurements of flow-mediated dilation have been reported to be impaired in pregnant women with established PE or those who develop PE later in pregnancy when compared with women with normotensive pregnancies.[49,50,59–61]

*Inflammation.* Inflammation has been implicated in both depression and PE. Studies have found increased levels of inflammatory markers to be associated with both depression and PE. For example, outside of pregnancy, commonly studied inflammatory markers, such as interleukin-1, interleukin-6, and C-reactive protein, have been shown to be positively associated with depression.[62] In pregnancy specifically, individuals with a history of depression have increased plasma C-reactive protein and glycoprotein acetyls.[63] Similarly, increased levels of these markers have been shown to be associated with PE.[64,65]

*Oxidative stress.* Markers of oxidative stress have also been studied in both depression and PE. In the general population, depression has been shown to be associated with increased oxidative stress and reduced antioxidant activity.[66] Furthermore, one study found that antenatal depression was significantly associated with increased levels of 8-isoprostane, a specific biomarker of oxidative stress.[67] Likewise, individuals with PE have elevated markers of oxidative stress, including 8-isoprostane as well as malondialdehyde and prostaglandin F2$\alpha$.[64,68]

The well-established relationships between inflammation, oxidative stress, and vascular function and the risk factors associated with both depression and PE

(*i.e.*, obesity and hypertension)[55,69,70] suggest that these factors may contribute as underlying risk factors between depression and PE. These similarities underscore the importance to better understand these mechanisms, so preventative and therapeutic strategies could be developed to improve maternal health.
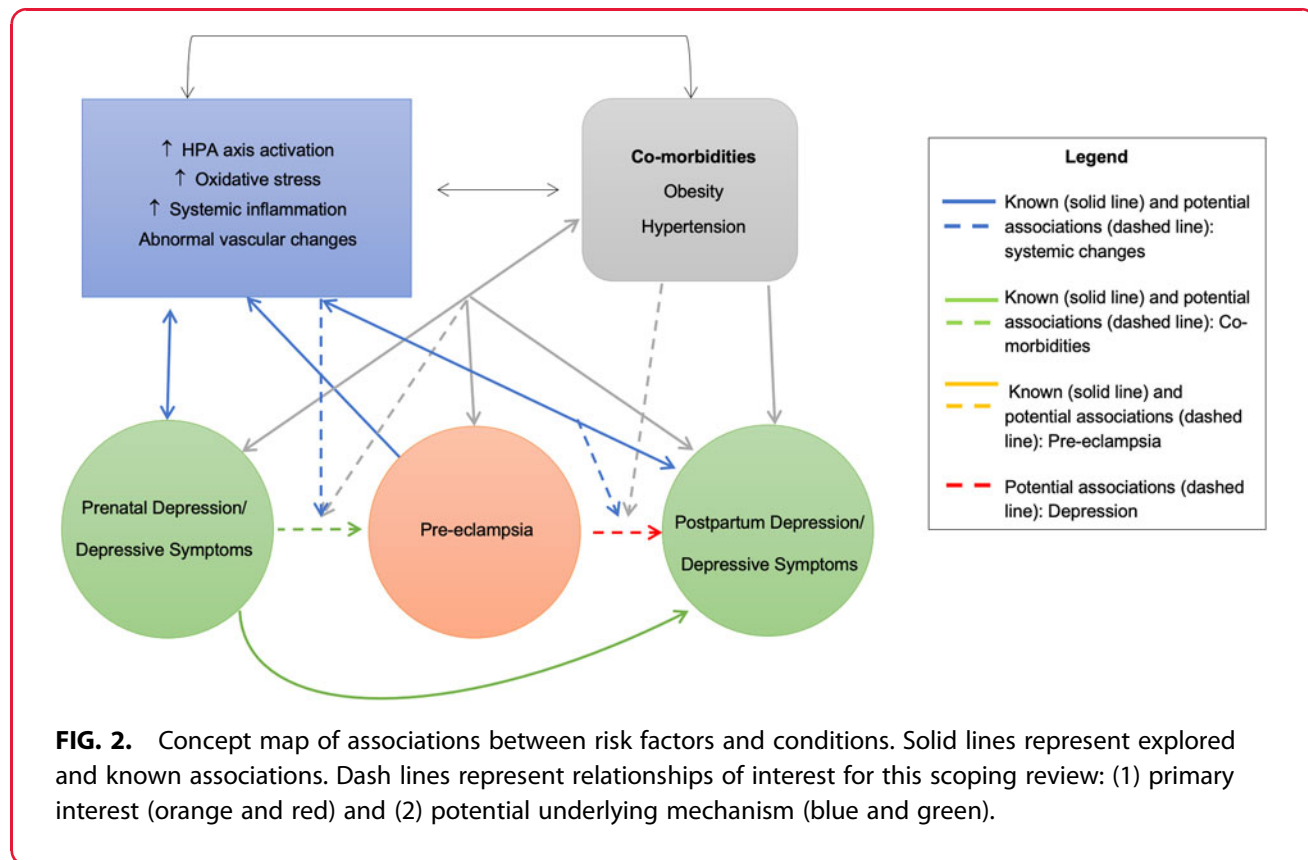
## Discussion

The scoping review addressing the first objective of this study summarized research findings regarding the association between depression and PE and found conflicting results, although these inconsistent results may reflect the challenges of "standardizing" evaluations during a complex time period. Contextually, pregnancy can span from conception until the delivery of the newborn, suggesting various time points where depressive symptoms can be assessed (*i.e.,* 1st, 2nd, and 3rd trimester). Fluctuating moods and emotions between different stages of the pregnancy may lead to varying levels of negative affect and thus rendering some associations significant and others insignificant. For this reason, the prevalence of depression in pregnancy may be over- or underestimated, depending on the timing of assessment.

The definition of the postpartum period varied from immediately postdelivery, 1–6 months after delivery, and up to several years after the indexed delivery. Despite the varying time of assessment, the majority of the studies reported that there was an increased risk of experiencing postpartum depression following PE. These findings aligned with the meta-analysis performed by Caropreso et al,[33] which reported that 8 of 13 studies observed associations between PE and postpartum depression or depression outside the perinatal period.

As most of the studies included in our scoping review were epidemiological and thus only assessed the prevalence and association of these disorders in pregnant women, following a secondary literature search, we outlined some of the cardiovascular and metabolic factors associated with both pathologies (*e.g.,* preexisting obesity, increased systemic inflammation, oxidative stress, vascular changes, and endothelial dysfunction) that may contribute to the common underlying etiologies between depression and PE. The complex relationship between these pathologies and risk factors are given in Figure 2.

Many of these risk factors interact with one another and may be linked in a vicious cycle affecting overall



**FIG. 2.** Concept map of associations between risk factors and conditions. Solid lines represent explored and known associations. Dash lines represent relationships of interest for this scoping review: (1) primary interest (orange and red) and (2) potential underlying mechanism (blue and green).

cardiometabolic health. For example, both PE and depression are associated with increased rates of obesity and cardiovascular disease, which too share many of these underlying risk factors.[41,44,71–73] There is substantial evidence from both animal and human studies that depression and cardiovascular disease are linked through changes in oxidative stress, hyperactivation of the hypothalamic–pituitary–adrenal axis and the immune system.[71,74–76] These changes are also considered mechanistic links between depression and obesity.[41] PE has been associated with an imbalance between the antioxidant defense system and the production of reactive oxygen species, which then leads to an increase in generalized inflammatory processes and endothelial dysfunction.[77,78] Endothelial dysfunction in women with PE has also been associated with significantly higher levels of oxidative stress, markers of systemic inflammation, and overactivation of the hypothalamic–pituitary–adrenal axis.[79,80]

Risk factors such as vascular endothelial dysfunction, as evidenced by reductions to the flow-mediated dilation response, are tightly linked with prooxidant and proinflammatory environments across a wide of array of conditions. The "positive feedback loop" that many investigators have identified in linking elevated oxidant stress with chronic inflammation can have the impact of reducing mediators of vascular function such as nitric oxide and prostacyclin bioavailability and increase vascular production of constrictor metabolites such as thromboxane $A_2$ among other metabolites of arachidonic acid. Each of these potential contributors may act to increase vascular resistance within human subjects and alter patterns of cerebral perfusion—which has been identified as a likely contributor to cognitive impairments including depressive symptoms.

In addition, reductions to arterial and vascular wall distensibility will have significant impacts on the penetrance of pulse wave hemodynamics deeper into the cerebrovascular circulation and has been implicated in cerebrovascular network remodeling impairing mass transport and exchange within the microcirculation. Taken together, this constellation of vascular impairments and elevated risk factor profiles may represent a significant contributor to the emergence of depressive symptoms, potentially of vascular origin. This is an area of investigation that will require significantly more study in the coming years to better understand how to identify and support women who may be at higher risk for these conditions and help alleviate subsequent complications.

Limitations of this scoping review include restricting to English-only articles from three databases and including all eligible studies without evaluation of the quality or size of the study. In addition, to specifically assess the association between depression during pregnancy and PE, this review excluded any studies that evaluated the possible mediating effects of antidepressant medications. Strengths of this study include the differentiation between prenatal and postpartum depression and the abstraction and synthesis of information related to potential underlying causal mechanisms. Previous reviews on this topic have only assessed the relationship between either prenatal depressive symptoms or postpartum depressive symptoms and PE. Furthermore, this scoping review focused on identifying common underlying cardiovascular risk factors that may contribute to the relationship between the two conditions. This is the only scoping review thus far that investigates the available literature on depression and PE throughout the perinatal period with consideration for common underlying risk factors.

## Conclusion

In conclusion, pregnant women with prenatal depressive symptoms may be at increased risk of developing PE and women who developed PE are at increased risk of developing postpartum depressive symptoms. Moreover, this review highlighted the cardiovascular and metabolic changes that may be contributing to the relationship between the two pathologies and may be useful as early pregnancy indicators of those who are at a higher risk for adverse pregnancy outcomes. Although universal screening for prenatal depression and PE is beneficial and are goals for many obstetrical settings, an overall assessment of cardiometabolic health in early pregnancy may be more useful to detect those who are most at risk for depression and/or PE and their associated complications.

## Authors' Contributions

M.Y.: conceptualization, methodology, investigation, formal analysis, writing—original draft, writing—review and editing, visualization. S.B.: methodology, investigation, formal analysis, writing—original draft, writing—review and editing, visualization. B.d.V.: conceptualization, methodology, formal analysis, writing—review and editing, supervision, project administration. G.E.: conceptualization, methodology, formal analysis, writing—review and editing, supervision, project administration. J.C.F.: conceptualization, methodology,

formal analysis, writing—review and editing, supervision. S.J.F.: conceptualization, methodology, formal analysis, writing—review and editing, supervision, project administration.

## References

1. Butalia S, Audibert F, Cote AM, et al. Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy. Can J Cardiol 2018;34(5):526–531; doi: 10.1016/j.cjca.2018.02.021
2. Magee LA, Pels A, Helewa M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: Executive summary. J Obst Gynaecol Canada 2014;36(5):416–438; doi: 10.1016/s1701-2163(15)30588-0
3. Canada PHAo. Maternal hypertension in Canada. Canada PHAo: Ottawa, Canada; 2014.
4. Department of Health (2020) Clinical Practice Guidelines: Pregnancy Care. Canberra: Australian Government Department of Health. "Risk of preeclampsia" Part D, Section 26. https://www.health.gov.au/resources/pregnancy-care-guidelines/part-d-clinical-assessments/risk-of-preeclampsia [Last accessed: October 18, 2022].
5. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016; 387(10026):1377–1396; doi: 10.1016/S0140-6736(16)30054-X
6. Wijeratne DT, Lajkosz K, Brogly SB, et al. Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: A population-based cohort study in Ontario, Canada. Circ Cardiovasc Qual Outcomes 2018;11(2):e003973; doi: 10.1161/CIRCOUTCOMES.117.003973
7. Berger H, Melamed N, Murray-Davis B, et al. Prevalence of pre-pregnancy diabetes, obesity, and hypertension in Canada. J Obstet Gynaecol Can 2019;41(11):1579.e2–1588.e2; doi: 10.1016/j.jogc.2019.01.020
8. Provencher C, Milan A, Hallman S, et al. Report on the Demographic Situation in Canada: Fertility Overview, 2012–2016. In Her Majesty the Queen in Right of Canada as represented by the Minister of Industry, 2018. Minister of Industry Canada: Ottawa, Canada; 2018.
9. Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci 2015;40(4):219–221; doi: 10.1503/jpn.150205
10. Table HHD. Perinatal Mental Health Toolkit for Ontario Public Health Units. Queen's Printer for Ontario: Toronto, Canada; 2018.
11. Lanes A, Kuk JL, Tamim H. Prevalence and characteristics of postpartum depression symptomatology among Canadian women: A cross-sectional study. BMC Public Health 2011;11(302):302; doi: 10.1186/1471-2458-11-302
12. Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. The impact of maternal depression during pregnancy on perinatal outcomes: A systematic review and meta-analysis. J Clin Psychiatry 2013;74(4):e321–e341; doi: 10.4088/JCP.12r07968
13. Molyneaux E, Poston L, Khondoker M, et al. Obesity, antenatal depression, diet and gestational weight gain in a population cohort study. Arch Womens Ment Health 2016;19(5):899–907; doi: 10.1007/s00737-016-0635-3
14. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. Int J Soc Res Methodol 2005;8(1):19–32; doi: 10.1080/1364557032000119616
15. Kurki T, Hiilesmaa V, Raitasalo R, et al. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000;95(4):487–490; doi: 10.1016/s0029-7844(99)00602-x
16. Bansil P, Kuklina EV, Meikle SF, et al. Maternal and fetal outcomes among women with depression. J Womens Health (Larchmt) 2010;19(2):329–334; doi: 10.1089/jwh.2009.1387
17. Kharaghani R, Geranmaye M, Janani L, et al. Preeclampsia and depression: A case-control study in Tehran. Arch Gynecol Obstet 2012;286(1):249–253; doi: 10.1007/s00404-012-2260-3
18. Qiu C, Sanchez SE, Lam N, et al. Associations of depression and depressive symptoms with preeclampsia: Results from a Peruvian case-control study. BMC Womens Health 2007;7(15); doi: 10.1186/1472-6874-7-15
19. Qiu C, Williams MA, Calderon-Margalit R, et al. Preeclampsia risk in relation to maternal mood and anxiety disorders diagnosed before or during early pregnancy. Am J Hypertens 2009;22(4):397–402; doi: 10.1038/ajh.2008.366
20. Kim DR, Sockol LE, Sammel MD, et al. Elevated risk of adverse obstetric outcomes in pregnant women with depression. Arch Womens Ment Health 2013;16(6):475–482; doi: 10.1007/s00737-013-0371-x
21. Ghaffar S, Rizvi S, Saeed G, et al. Frequency of depression among hospitalized pregnant females for obstetrics risk. Pakistan J Med Health Sci 2016;10(3):898–901; WOS:000405495600059.
22. Palmsten K, Setoguchi S, Margulis AV, et al. Elevated risk of preeclampsia in pregnant women with depression: Depression or antidepressants? Am J Epidemiol 2012;175(10):988–997; doi: 10.1093/aje/kwr394
23. Vollebregt KC, van der Wal MF, Wolf H, et al. Is psychosocial stress in first ongoing pregnancies associated with pre-eclampsia and gestational hypertension? BJOG 2008;115(5):607–615; doi: 10.1111/j.1471-0528.2008.01665.x
24. Hu R, Li Y, Zhang Z, et al. Antenatal depressive symptoms and the risk of preeclampsia or operative deliveries: A meta-analysis. PLoS One 2015; 10(3):e0119018; doi: 10.1371/journal.pone.0119018
25. Zhang S, Ding Z, Liu H, et al. Association between mental stress and gestational hypertension/preeclampsia: A meta-analysis. Obstet Gynecol Surv 2013;68(12):825–834; doi: 10.1097/OGX.0000000000000001
26. Chen L, Wang X, Ding Q, et al. Development of postpartum depression in pregnant women with preeclampsia: A retrospective study. Biomed Res Int 2019;2019:9601476; doi: 10.1155/2019/9601476
27. Mbarak B, Kilewo C, Kuganda S, et al. Postpartum depression among women with pre-eclampsia and eclampsia in Tanzania; a call for integrative intervention. BMC Pregnancy Childbirth 2019;19(1):270; doi: 10.1186/s12884-019-2395-3
28. Strapasson MR, Ferreira CF, Ramos JGL. Associations between postpartum depression and hypertensive disorders of pregnancy. Int J Gynaecol Obstet 2018;143(3):367–373; doi: 10.1002/ijgo.12665
29. Youn H, Lee S, Han SW, et al. Obstetric risk factors for depression during the postpartum period in South Korea: A nationwide study. J Psychosom Res 2017;102:15–20; doi: 10.1016/j.jpsychores.2017.09.003
30. Auger N, Low N, Paradis G, et al. Preeclampsia and the longitudinal risk of hospitalization for depression at 28 years. Soc Psychiatry Psychiatr Epidemiol 2021;56(3):429–436; doi: 10.1007/s00127-020-01920-x
31. Bergink V, Laursen TM, Johannsen BM, et al. Pre-eclampsia and first-onset postpartum psychiatric episodes: A Danish population-based cohort study. Psychol Med 2015;45(16):3481–3489; doi: 10.1017/S0033291715001385
32. Hoedjes M, Berks D, Vogel I, et al. Postpartum depression after mild and severe preeclampsia. J Womens Health (Larchmt) 2011;20(10):1535–1542; doi: 10.1089/jwh.2010.2584
33. Caropreso L, de Azevedo Cardoso T, Eltayebani M, et al. Preeclampsia as a risk factor for postpartum depression and psychosis: A systematic review and meta-analysis. Arch Womens Ment Health 2020;23(4):493–505; doi: 10.1007/s00737-019-01010-1
34. Thombre MK, Talge NM, Holzman C. Association between pre-pregnancy depression/anxiety symptoms and hypertensive disorders of pregnancy. J Womens Health (Larchmt) 2015;24(3):228–236; doi: 10.1089/jwh.2014.4902
35. Mommersteeg PM, Drost JT, Ottervanger JP, et al. Long-term follow-up of psychosocial distress after early onset preeclampsia: The Preeclampsia Risk EValuation in FEMales cohort study. J Psychosom Obstet Gynaecol 2016;37(3):101–109; doi: 10.3109/0167482X.2016.1168396

36. Katsipi I, Stylianou K, Petrakis I, et al. The use of pulse wave velocity in predicting pre-eclampsia in high-risk women. Hypertens Res 2014;37(8): 733–740; doi: 10.1038/hr.2014.62

37. Wu Y, Sun D, Wang B, et al. The relationship of depressive symptoms and functional and structural markers of subclinical atherosclerosis: A systematic review and meta-analysis. Eur J Prev Cardiol 2018;25(7): 706–716; doi: 10.1177/2047487318764158

38. Spradley FT, Palei AC, Granger JP. Increased risk for the development of preeclampsia in obese pregnancies: Weighing in on the mechanisms. Am J Physiol Regul Integr Comp Physiol 2015;309(11):R1326–R1343; doi: 10.1152/ajpregu.00178.2015

39. Steinig J, Nagl M, Linde K, et al. Antenatal and postnatal depression in women with obesity: A systematic review. Arch Womens Ment Health 2017;20(4):569–585; doi: 10.1007/s00737-017-0739-4

40. Holton S, Fisher J, Nguyen H, et al. Pre-pregnancy body mass index and the risk of antenatal depression and anxiety. Women Birth 2019;32(6): e508–e514; doi: 10.1016/j.wombi.2019.01.007

41. Milaneschi Y, Simmons WK, van Rossum EFC, et al. Depression and obesity: Evidence of shared biological mechanisms. Mol Psychiatry 2019; 24(1):18–33; doi: 10.1038/s41380-018-0017-5

42. Bodnar LM, Catov JM, Klebanoff MA, et al. Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. Epidemiology (Cambridge, Mass) 2007;18(2):234–239; doi: 10.1097/01.ede.0000254119.99660.e7

43. Magann EF, Doherty DA, Sandlin AT, et al. The effects of an increasing gradient of maternal obesity on pregnancy outcomes. Aust N Z J Obstet Gynaecol 2013;53(3):250–257; doi: 10.1111/ajo.12047

44. Eastabrook G, Aksoy T, Bedell S, et al. Preeclampsia biomarkers: An assessment of maternal cardiometabolic health. Pregnancy Hypertens 2018;13(204–213); doi: 10.1016/j.preghy.2018.06.005

45. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. Biol Psychiatry 2011;69(8):795–803; doi: 10.1016/j.biopsych.2010.12.034

46. Estensen ME, Remme EW, Grindheim G, et al. Increased arterial stiffness in pre-eclamptic pregnancy at term and early and late postpartum: A combined echocardiographic and tonometric study. Am J Hypertens 2013;26(4):549–556; doi: 10.1093/ajh/hps067

47. van Sloten TT, Boutouyrie P, Tafflet M, et al. Carotid artery stiffness and incident depressive symptoms: The paris prospective study III. Biol Psychiatry 2019;85(6):498–505; doi: 10.1016/j.biopsych.2018.09.018

48. Bernstein IM, Hale SA, Badger GJ, et al. Differences in cardiovascular function comparing prior preeclamptics with nulliparous controls. Pregnancy Hypertens 2016;6(4):320–326; doi: 10.1016/j.preghy.2016.07.001

49. Foo FL, McEniery CM, Lees C, et al. Assessment of arterial function in pregnancy: Recommendations of the International Working Group on Maternal Hemodynamics. Ultrasound Obstet Gynecol 2017;50(3):324–331; doi: 10.1002/uog.17565

50. Harville EW, Juonala M, Viikari JSA, et al. Pregnancy complications and later vascular ultrasound measures: A cohort study. Pregnancy Hypertens 2017;10:171–176; doi: 10.1016/j.preghy.2017.08.001

51. Khalil A, Garcia-Mandujano R, Maiz N, et al. Longitudinal changes in maternal hemodynamics in a population at risk for pre-eclampsia. Ultrasound Obstet Gynecol 2014;44(2):197–204; doi: 10.1002/uog.13367

52. Mannaerts D, Faes E, Cornette J, et al. Low-flow mediated constriction as a marker of endothelial function in healthy pregnancy and preeclampsia: A pilot study. Pregnancy Hypertens 2019;17:75–81; doi: 10.1016/j.preghy.2019.02.001

53. Oylumlu M, Oylumlu M, Yuksel M, et al. A simple method for the assessment of arterial stiffness in pre-eclamptic patients. Clin Exp Hypertens 2014;36(8):531–537; doi: 10.3109/10641963.2014.913608

54. Savvidou MD, Kaihura C, Anderson JM, et al. Maternal arterial stiffness in women who subsequently develop pre-eclampsia. PLoS One 2011;6(5): e18703; doi: 10.1371/journal.pone.0018703

55. Tihtonen KM, Koobi T, Uotila JT. Arterial stiffness in preeclamptic and chronic hypertensive pregnancies. Eur J Obstet Gynecol Reprod Biol 2006;128(1–2):180–186; doi: 10.1016/j.ejogrb.2005.12.026

56. Webster LM, Myers JE, Nelson-Piercy C, et al. Longitudinal changes in vascular function parameters in pregnant women with chronic hypertension and association with adverse outcome: A cohort study. Ultrasound Obstet Gynecol 2019;53(5):638–648; doi: 10.1002/uog.19021

57. Cooper DC, Tomfohr LM, Milic MS, et al. Depressed mood and flow-mediated dilation: A systematic review and meta-analysis. Psychosom Med 2011;73(5):360–369; doi: 10.1097/PSY.0b013e31821db79a

58. Moran LJ, Wilson CJ, Buckley JD, et al. Changes in endothelial function and depression scores are associated following long-term dietary intervention: A secondary analysis. Nutrition 2013;29(10):1271–1274; doi: 10.1016/j.nut.2013.03.023

59. Malhotra AS, Goel P, Chaudhary A, et al. Serial profile of flow-mediated dilatation in primigravida for prediction of preeclampsia and gestational hypertension. Hypertens Pregnancy 2018;37(4):212–219; doi: 10.1080/10641955.2018.1524480

60. Oliveira OP, Araujo Junior E, Lima JW, et al. Flow-mediated dilation of brachial artery and endothelial dysfunction in pregnant women with preeclampsia: A case control study. Minerva Ginecol 2015;67(4):307–313. PMID: 25476264.

61. Tomimatsu T, Mimura K, Matsuzaki S, et al. Preeclampsia: Maternal systemic vascular disorder caused by generalized endothelial dysfunction due to placental antiangiogenic factors. Int J Mol Sci 2019;20(17); doi: 10.3390/ijms20174246

62. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med 2009; 71(2):171–186; doi: 10.1097/PSY.0b013e3181907c1b

63. Lahti-Pulkkinen M, Girchenko P, Robinson R, et al. Maternal depression and inflammation during pregnancy. Psychol Med 2020;50(11):1839–1851; doi: 10.1017/S0033291719001909

64. Ouyang YQ, Li SJ, Zhang Q, et al. Interactions between inflammatory and oxidative stress in preeclampsia. Hypertens Pregnancy 2009;28(1):56–62; doi: 10.1080/10641950802233064

65. Guven MA, Coskun A, Ertas IE, et al. Association of maternal serum CRP, IL-6, TNF-alpha, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birth weight. Hypertens Pregnancy 2009;28(2):190–200; doi: 10.1080/10641950802601179

66. Palta P, Samuel LJ, Miller ER, 3rd, et al. Depression and oxidative stress: Results from a meta-analysis of observational studies. Psychosom Med 2014;76(1):12–19; doi: 10.1097/PSY.0000000000000009

67. Venkatesh KK, Meeker JD, Cantonwine DE, et al. Association of antenatal depression with oxidative stress and impact on spontaneous preterm birth. J Perinatol 2019;39(4):554–562; doi: 10.1038/s41372-019-0317-x

68. Genc H, Uzun H, Benian A, et al. Evaluation of oxidative stress markers in first trimester for assessment of preeclampsia risk. Arch Gynecol Obstet 2011;284(6):1367–1373; doi: 10.1007/s00404-011-1865-2

69. Mandviwala T, Khalid U, Deswal A. Obesity and cardiovascular disease: A risk factor or a risk marker? Curr Atheroscler Rep 2016;18(5):21; doi: 10.1007/s11883-016-0575-4

70. Levy BI, Schiffrin EL, Mourad JJ, et al. Impaired tissue perfusion: A pathology common to hypertension, obesity, and diabetes mellitus. Circulation 2008;118(9):968–976; doi: 10.1161/CIRCULATIONAHA.107.763730

71. Bradley SM, Rumsfeld JS. Depression and cardiovascular disease. Trends Cardiovasc Med 2015;25(7):614–622; doi: 10.1016/j.tcm.2015.02.002

72. Cohen BE, Edmondson D, Kronish IM. State of the art review: Depression, stress, anxiety, and cardiovascular disease. Am J Hypertens 2015;28(11): 1295–1302; doi: 10.1093/ajh/hpv047

73. Jha MK, Qamar A, Vaduganathan M, et al. Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2019;73(14):1827–1845; doi: 10.1016/j.jacc.2019.01.041

74. Fioranelli M, Bottaccioli AG, Bottaccioli F, et al. Stress and inflammation in coronary artery disease: A review psychoneuroendocrineimmunology-based. Front Immunol 2018;9:2031; doi: 10.3389/fimmu.2018.02031

75. Baune BT, Stuart M, Gilmour A, et al. The relationship between subtypes of depression and cardiovascular disease: A systematic review of biological models. Transl Psychiat 2012;2:e92; doi: 10.1038/tp.2012.18

76. Lin D, Wang L, Yan S, et al. The role of oxidative stress in common risk factors and mechanisms of cardio-cerebrovascular ischemia and depression. Oxid Med Cell Longev 2019;2019:2491927; doi: 10.1155/2019/2491927

77. Tenorio MB, Ferreira RC, Moura FA, et al. Cross-talk between oxidative stress and inflammation in preeclampsia. Oxid Med Cell Longev 2019; 2019:8238727; doi: 10.1155/2019/8238727

78. Adu-Bonsaffoh K, Antwi DA, Gyan B, et al. Endothelial dysfunction in the pathogenesis of pre-eclampsia in Ghanaian women. BMC Physiol 2017; 17(1):5; doi: 10.1186/s12899-017-0029-4

79. Logue OC, George EM, Bidwell GL, 3rd. Preeclampsia and the brain: Neural control of cardiovascular changes during pregnancy and neurological outcomes of preeclampsia. Clin Sci (Lond) 2016;130(16):1417–1434; doi: 10.1042/CS20160108

80. Mannaerts D, Faes E, Cos P, et al. Oxidative stress in healthy pregnancy and preeclampsia is linked to chronic inflammation, iron status and vascular function. PLoS One 2018;13(9):e0202919; doi: 10.1371/journal.pone.0202919

81. Gaugler-Senden IPM, Duivenvoorden HJ, Filius A, et al. Maternal psychosocial outcome after early onset preeclampsia and preterm birth. J Matern Neonatal Med 2012;25:272–276; doi: 10.3109/14767058.2011.573829

## Abbreviations Used

ACOG = American College of Obstetrics and Gynecology
Aix = augmentation index (indices)
AOR = adjusted odds ratio
BDI = beck depression index
BMI = body mass index ($kg/m^2$)
CES-D = Centers for Epidemiologic Studies Depression Screener
CI = confidence interval
CVD = cardiovascular disease
DS/D = depressive symptoms/depression
EPDS = Edinburgh Postnatal Depression Scale
FMD = flow-mediated dilation
GDM = gestational diabetes mellitus
GH = gestational hypertension
HDP = hypertensive disorders of pregnancy
HPA = hypothalamic–pituitary axis
HR = hazards ratio
ICD-9 = International Classification of Disease, Version 9
ISSHP = International Society for the Study of Hypertension in Pregnancy
IUGR = Intrauterine growth restriction
LMP = last menstrual period
MDD = major depressive disorder
MNH = Muhimbili National Hospital
NICU = neonatal intensive care unit
OR = odds ratio
PE = preeclampsia
PHQ-9 = Patient Health Questionnaire-9
PPD = postpartum depression
PTB = pre-term birth
PWV = pulse-wave velocity
RR = relative risk