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Predictors of Preeclampsia and Its Impact on Perinatal Outcomes

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KEYWORDS

preeclampsia, predictors, perinatal mortality, preterm birth, neonatal intensive care unit, meta-analysis.

ABSTRACT:

Preeclampsia (PE) is a multisystem hypertensive disorder of pregnancy associated with substantial maternal and perinatal morbidity and mortality (Steegers et al., 2010; Magee et al., 2022). To identify predictors of PE and quantify the association between PE and adverse perinatal outcomes. We conducted a systematic review and meta-analysis following PRISMA 2020. PubMed, Scopus, and Web of Science were searched for observational studies evaluating PE predictors and/or PE-related perinatal outcomes. Random-effects meta-analysis was performed when ≥3 studies reported clinically comparable definitions and effect measures. Fifteen studies were included (cohort, nested case–control, and population-based designs) from high- and middle-income settings. Narrative synthesis identified recurring predictors of PE and adverse outcomes including obesity, nulliparity, multifetal gestation, prior PE, and severity markers (e.g., HELLP features). In pooled analyses, PE was associated with higher risk of perinatal death/stillbirth (RR 1.28, 95% CI 1.10–1.48; I^2=0%). PE was strongly associated with very preterm birth <34 weeks (RR 3.43, 95% CI 2.62–4.49; I^2=0%) and NICU admission (RR 3.87, 95% CI 2.80–5.35; I^2=0%). Severe versus non-severe PE was associated with increased composite adverse perinatal outcomes (RR 1.93, 95% CI 1.19–3.12; I^2=86.9%). Publication bias was not formally assessed due to <10 studies per outcome. PE substantially increases risks of perinatal death, very preterm birth, and NICU admission. Early risk identification and severity-aware management are essential to reduce preventable adverse outcomes.

Introduction

Overview of Preeclampsia

Preeclampsia is a pregnancy-related, multisystemic disease and a major cause of maternal and perinatal morbidity and mortality all over the world (Steegers et al., 2010). It is clinically defined as new-onset hypertension post-mid-pregnancy with maternal organ dysfunction (e.g. renal, hepatic, neurologic, or hematologic complications) and/or uteroplacental dysfunction (e.g. fetal growth restriction) and can either be associated or unassociated with proteinuria (Magee et al., 2022). Modern international practice points at the fact that preeclampsia is no longer about hypertension + proteinuria, but a symptom of systemic endothelial dysfunction and inflammatory response, which is often based on incorrect placentation and maternal vascular maladaptation (Steegers et al., 2010; Magee et al., 2022).

The idea of pathophysiology is usually described in two phases (Steegers et al., 2010). Suboptimal trophoblast

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invasion and poor remodeling of the spiral artery decrease placental perfusion because of ischemia and oxidative stress in most instances, especially early-onset disease. The dysfunction in the placenta is linked to the presence of increased antiangiogenic factors (in particular, soluble fms-like tyrosine kinase-1 [sFlt-1]) and decreased proangiogenic factors (including placental growth factor [PlGF]) that cause extensive maternal endothelial damage, vasoconstriction, and capillary leak (Steegers et al., 2010). Disease at an early-onset (frequently necessitating prenatal delivery less than 34 weeks) is more commonly associated with more severe placental pathology, fetal growth retardation, and iatrogenic prematurity, but late-onset disease may be less overtly placental impaired, but still with a massive maternal and neonatal risk (Steegers et al., 2010; Magee et al., 2022). Since delivery of the placenta is the ultimate treatment, clinicians tend to balance maternal stabilization and fetal maturity and, as a result, prevention and early risk stratification become the focus of the enhanced outcomes (Magee et al., 2022).

Global Burden & Public Health Importance

Preeclampsia has a significant target population in terms of pregnancy across the globe and promotes maternal and newborn mortality through its significant contribution to preventable death (Steegers et al., 2010; Xiong et al., 2025). A more recent systematic review and meta-analysis gave the world prevalence of about 4.4 percent, but its estimates per region and method of study are variable (Vera-Ponce et al., 2025). The burden is not evenly distributed as the global studies of hypertensive disorders of pregnancy show the existence of the persistent regional imbalance with higher mortality and disability in the environment with low sociodemographic index where delayed diagnosis, the inability to refer, and inadequate neonatal care compound risks (Xiong et al., 2025). These differences are important since preeclampsia can be commonly identified through regular antenatal care, and most of the adverse effects can be avoided when the condition is identified early enough, monitored, and the delivery is encouraged (Magee et al., 2022). Preeclampsia is linked to higher utilization of medically indicated preterm births and neonatal intensive care and high-risk of cardiovascular morbidity in the long-term among mothers (Steegers et al., 2010) but the problem extends beyond pregnancy.

Known & Suspected Predictors

The multifactorial etiology of preeclampsia is indicated by predictors of this condition (Bartsch et al., 2016; Magee et al., 2022). The systematic evidence suggests the maternal history and baseline characteristics as some of the simplest and most effective predictors in the early part of pregnancy (Bartsch et al., 2016). Risk factors are preeclampsia in the past, chronic hypertension, pregestational diabetes, kidney disease, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome, in addition to the nulliparity, old age of the mother, preexisting preeclampsia in the family, and multiple pregnancies (Bartsch et al., 2016; Magee et al., 2022). Increased cardiometabolic risk, including overweight and obesity, is gaining more significance; cohort meta-analytic results indicate that there is a risk gradient with increasing probability of preeclampsia in overweight and obese women before pregnancy (He et al., 2020).

In addition to the clinical history, screening strategies are becoming more relevant to include biophysical and biochemical indicators (Magee et al., 2022). Angiogenic biomarkers, especially the sFlt-1/PlGF ratio, are the indicators of placental dysfunction and can be used to predict complications and triage in hypertensive disorders of pregnancy, but standardization and external validation have become an issue (Bucher et al., 2024). The clinical importance of prediction is supported by the evidence that intervention using prediction to prevent preterm preeclampsia can be reduced; a large, randomized study found that low-dose aspirin started early in pregnancy reduced preterm preeclampsia risk in women who were at high risk due to combined screening (Rolnik et al., 2017). Nevertheless, the effect of predictors and practical thresholds may change in populations due to the varying baseline risks, comorbidities, access to care, and how the disease is diagnosed (Magee et al., 2022).

Impact on Perinatal Outcomes

There is strong correlation between preeclampsia and adverse perinatal outcome that is mostly mediated by uteroplacental insufficiency and early delivery due to medical reasons (Steegers et al., 2010). The frequent ones are preterm birth, low birth weight/small-for-gestational-age (SGA) newborns, fetal growth

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retardation, NICU hospitalization, and perinatal mortality (Steegers et al., 2010; Teka et al., 2023). Growth restriction and extreme prematurity represent the primary causes of neonatal morbidity and mortality, and they are specifically related to early-onset disease (Teka et al., 2023). The heterogeneity in presentation and outcome definitions makes it challenging to predict the development of severe maternal or perinatal complications in the face of the group of maternal disease, even when the disease is known and treated, therefore the uncertainty may contribute to the escalation of care or iatrogenic prematurity (Magee et al., 2022; Bucher et al., 2024). The difference between outcome-specific risks by onset and severity might be quantified to support different levels of surveillance and referral thresholds as well as timing-of-delivery decisions (Magee et al., 2022).

Rationale & Knowledge Gap

Despite the numerous reported predictors, evidence base is still fragmented depending on region, study designs, and changing definitions of diagnosis (Magee et al., 2022). Previous reviews have either looked at clinical risk factors or at prognostic instruments in women who have already received a diagnosis of hypertensive disorders, with little consideration of the strength of predictors and downstream perinatal outcome in the same analytic model (Bartsch et al., 2016; Bucher et al., 2024). Moreover, the lack of comparability and pooling is caused by heterogeneity in definitions of preeclampsia subtypes, as well as perinatal outcomes (Bucher et al., 2024). This encourages the synthesis of meta-analysis with the same criteria in different settings.

Objectives

The goals of this meta-analysis are to (1) determine and measure the relationships between the previously known and possible predictors (maternal demographic factors, obstetric history, medical comorbidities, and the use of selected screening markers where feasible) and the risk of developing preeclampsia; and (2) approximate the impact of preeclampsia on the key perinatal outcomes, such as preterm birth, low birth weight/SGA, fetal growth restriction, NICU hospitalization, stillbirth, and neonatal death. Where available, we will investigate the sources of heterogeneity (e.g., early- vs late-onset disease, setting of the study and criterion of diagnosis) to elucidate the differences in predictor-risk relationships and the effects of the perinatal on the populations and settings.

Methods

Study Design

This paper was a systematic review and meta-analysis, which aimed to define the predictors of preeclampsia (PE) and to measure the effect of PE on perinatal outcomes. The review has been conducted according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guideline. The general process involved searching the database, elimination of duplicates, screening of titles and abstracts, screening of full-text eligibility, extraction of data, risk-of-bias appraisal and quantitative synthesis (meta-analysis) when two or more studies reported a similar exposure-outcome relationship. Figure 1 summarizes a PRISMA 2020 flow diagram that summarizes the study selection process.

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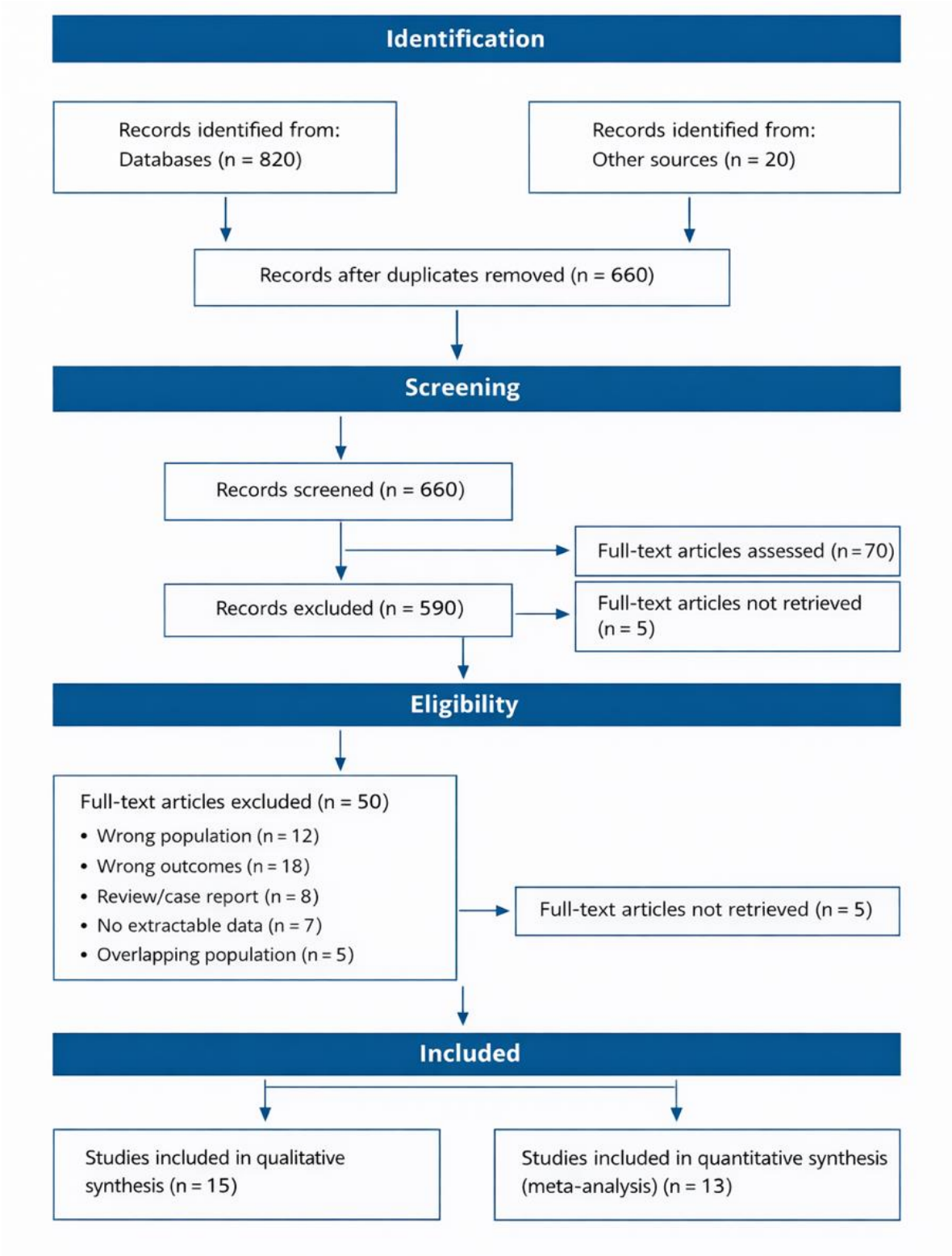
Figure 1: Prisma flow Diagram



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Eligibility Criteria (PICOS)

Population: Pregnant women (single or multi-gestations). Randomized controlled and cohort studies that reported predictor-PE or PE-outcome associations were included in the studies that were limited to clinical subgroups (e.g., prior PE, severe PE, or PE-only cohorts).

Exposure: PE as defined by each study, such as comparisons of (i) PE vs no PE, (ii) severe vs non-severe/mild PE (or PE with severe features vs without) and/or (iii) early- vs late-onset PE (usually <34 weeks). Predictors (e.g., BMI/obesity, parity, chronic hypertension, proteinuria, category of hemoglobin, biomarkers, obstetric history) were only pooled when the definitions and effect measures were similar enough otherwise findings were narratively summarized.

Comparator: PE-versus-no-PE or normotensive/no-PE pregnancies versus timely/non-timely PE versus mild/non-severe PE versus late-onset PE. In cases where more than one comparator strata were registered, clinically significant differences were induced to prevent counting the same person twice.

Outcomes: The primary outcomes were the perinatal mortality (stillbirth/ feta# death/ perinatal death according to the studies), preterm birth (<34 weeks when possible), NICU hospitalization, and SGA/FGR (below the 10th percentile). Such secondary outcomes were low Apgar score, neonatal asphyxia, neonatal near-miss, and composite adverse perinatal outcomes. Only clinically similar outcomes were aggregated instead of synthesized narratively.

Types of studies Cohorts (prospective/retrospective) and case-control (including nested) studies were eligible. The large cross-sectional studies were incorporated in cases where they provided an estimate of the effect that could be analyzed. Articles that lacked adequate data like reviews, editorials, case reports and conference abstracts were excluded. Duplicate reports were managed by keeping the most comprehensive/up to date report.

Search Strategy

A systematic literature search was performed in **PubMed**, **Scopus**, and **Web of Science** to identify eligible studies. The search strategy combined controlled vocabulary (where applicable) and free-text terms related to preeclampsia, predictors/risk factors, severity/timing, and perinatal outcomes. Core search concepts included: "preeclampsia" OR "pre-eclampsia" AND ("risk factor*" OR "predictor*" OR "severity" OR "early-onset" OR "late-onset") AND ("perinatal" OR "stillbirth" OR "fetal death" OR "neonatal death" OR "preterm" OR "NICU" OR "small for gestational age" OR "fetal growth restriction" OR "Apgar"). Database-specific syntax and filters were applied consistently, and reference lists of key eligible studies were hand-searched to identify additional reports.

The timeframe covered the period specified in the protocol (to be reported explicitly in the final manuscript), and only studies available as full-text articles were included. Search results from all databases were exported into a reference manager, duplicates were removed, and the remaining records proceeded to screening. The full selection process is summarized in the PRISMA flow diagram (**Figure 1**).

Study selection. Two reviewers independently screened titles and abstracts against the eligibility criteria. Full texts were retrieved for records deemed potentially eligible. Full-text eligibility was then assessed independently by the same reviewers. Discrepancies at any stage were resolved by discussion and consensus; when consensus could not be reached, a third reviewer adjudicated.

Data Extraction

A standardized data extraction form was developed and piloted. For each included study, the following were extracted: author/year; country/setting; study design; population characteristics; sample size; PE definition and classification (including severity or timing thresholds where applicable); predictor definitions; comparator groups; outcomes and outcome definitions; and the effect estimates reported.

Effect sizes were extracted as reported, including **odds ratios (OR)**, **risk ratios (RR)**, and their adjusted forms (**aOR**, **aRR**) with 95% confidence intervals. When multiple estimates were reported for the same predictor–outcome relationship (e.g., crude and adjusted), the adjusted estimate was preferred for the primary meta-analysis, and crude estimates were retained for sensitivity analyses when appropriate. Where a study reported multiple outcomes, each eligible outcome was

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extracted separately. Where studies reported composite outcomes, the composite definition was recorded and analyzed separately from individual outcomes. A summary of study characteristics is presented in Table 1.

For transparency and reproducibility, extracted covariate adjustments were recorded (e.g., maternal age, parity, BMI, diabetes, chronic hypertension, multiple gestation, socioeconomic measures), enabling stratified analyses based on adjusted versus unadjusted estimates and facilitating interpretation of confounding.

Statistical Analysis

Meta-analysis was performed when ≥3 studies reported comparable exposure definitions, outcomes, and effect measures. Random-effects models were used, analyzing estimates on the log scale with standard errors derived from 95% confidence intervals. ORs and RRs were not pooled together unless clinically justified; where necessary, analyses were stratified by effect measure type. Heterogeneity was assessed using I^2 and τ^2. Prespecified subgroup analyses included severe vs non-severe PE, early- vs late-onset PE, and setting (LMIC vs HIC). Sensitivity analyses included leave-one-out analyses and restriction to lower-risk-of-bias or adjusted estimates where feasible. Publication bias was assessed only when outcomes included ≥10 studies (funnel plot and small-study effect tests such as Egger's); otherwise, it was not formally evaluated. Analyses were conducted using standard meta-analysis software (e.g., R or Stata).

Results

Characteristics of included studies

The inclusion criteria were 15 studies including prospective and retrospective cohort and nested control-case studies, as well as population-based studies (Table 1). Most research was undertaken in high-income countries (United Kingdom, Sweden, United States, and Germany), and some were based on the middle-income countries (China, Brazil, and Ethiopia). The sample sizes were between 180 women up to over 2 million births. Predictors of preeclampsia (PE), PE severity (severe vs non-severe), PE timing (early- vs late-onset), and comparisons of the pregnancies complicated by PE to those not complicated by PE and predictors of adverse outcomes were also included in the exposures. Perinatal death or stillbirth, very preterm birth (<34 weeks), neonatal intensive care unit (NICU) hospitalization, small for gestational age (SGA) or fetal growth restriction (FGR), composite adverse perinatal outcomes, neonatal asphyxia, and severe maternal outcomes (maternal near-miss and/or maternal death) were the outcomes assessed.

Table 1. Characteristics of included studies

Study (Year)	Country / Setting	Study design	Sample size	Exposure / comparison	Perinatal outcomes assessed	Effect estimates reported
Li et al. (2018)	China	Multicenter retrospective cohort	1,396 women with preeclampsia	Number of maternal risk factors within PE	Composite severe adverse outcome, perinatal death, preterm birth, very low birth weight, neonatal asphyxia	OR
Yang et al. (2021)	Sweden & China	Population-based cohort	634,689 births	PE vs no PE; maternal predictors of PE	Stillbirth, preterm birth, low Apgar score	RR
Mayrink et al. (2019)	Brazil	Nested case–control	1,165 pregnancies (87 PE; 1,078 controls)	Early-pregnancy clinical	Preterm birth <34 weeks, NICU admission, SGA, low Apgar score	RR

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				predictors of PE		
Lian et al. (2025)	China	Retrospective cohort	1,715 women with PE	Hemoglobin category at admission	Postpartum hemorrhage, HELLP syndrome, neonatal asphyxia, NICU admission	OR
Bramham et al. (2011)	United Kingdom	Prospective cohort	500 women	History of early-onset PE	Recurrent PE, recurrent preterm birth	OR, RR
Li et al. (2025)	China	Retrospective cohort	351 women with severe PE	Gestational age, twin pregnancy, PlGF, cholesterol	Composite adverse pregnancy outcome	aOR
Bilano et al. (2014)	29 countries (WHO survey)	Multicountry cross-sectional analysis	276,388 deliveries	PE/eclampsia vs no hypertensive disorder	Maternal near-miss or death, perinatal mortality	OR
Menezes-Oliveira et al. (2016)	Brazil	Prospective cohort	180 pregnancies (90 PE; 90 controls)	Prior PE, race/ethnicity	PE occurrence, birthweight abnormalities	PR
Jikamo et al. (2022)	Ethiopia	Prospective cohort	730 pregnancies (363 PE; 367 controls)	Severe vs non-severe PE	Composite adverse perinatal outcome, perinatal death	aRR
Ton et al. (2020)	United States (California)	Population-based cohort	~2.02 million births	Mild vs severe PE vs no PE	Infant and maternal adverse outcomes	RR
Abalos et al. (2014)	29 countries (WHO survey)	Multicountry cross-sectional analysis	~314,623 deliveries	Hypertensive disorder categories	Maternal near-miss or death, perinatal mortality	OR
Lisonkova & Joseph (2013)	United States	Population-based cohort	456,668 births	Early-onset vs late-onset PE	Fetal death, severe neonatal morbidity, FGR	aOR
Ulfsdottir et al. (2023)	Sweden	National registry cohort	805,591 primiparous women	PE vs no PE	Perinatal death, Apgar <7, neonatal resuscitation, SGA	aOR
Mbah et al. (2010)	United States	Registry-based cohort	Population registry	Prior PE	Stillbirth, infant death	OR

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Bossung et al. (2020)	Germany	Population-based cohort	16,035 VLBW infants (<32 weeks)	PE/HELLP vs other causes of preterm birth	Neonatal death, IVH, NEC, PVL	OR

Predictors of preeclampsia and perinatal outcomes in individual studies

Some studies assessed predictors of PE or adverse outcomes that could not be pooled because of differences in study design (e.g. PE only cohorts), definition of predictors or reporting of outcomes.

Li et al. (2018) found in a multicenter cohort of women with PE in China that there was a distinct dose-response relationship between accruing maternal risk factors and severe adverse outcomes. Females with three or more risk factors were likely to have severe adverse outcomes, when compared to females with no risk factors (OR 2.75, 95% CI 1.05-7.18). The most predictive factor of perinatal death was HELLP syndrome. Pregnancy multiple and rural living were other risk factors which led to preterm childbirth and fetal distress.

Yang et al. (2021) conducted a population-based comparative study between Sweden and China on obesity, nulliparity, and multiple pregnancies found that these risk factors are strongly associated with PE. The prevalence of stillbirth was higher in the cases of PE-complicated pregnancies (4.6) in comparison to the non-PE cases (0.4).

According to the nested case-control study by Mayrink et al. (2019), which was conducted in Brazil, the PE-affected pregnancies were at risk of the very preterm birth (less than 34 weeks), SGA, and NICU admission. In PE-only cohorts, Lian et al. (2025) results showed that anemia at admission was markedly linked with postpartum hemorrhage (OR 3.80, 95% CI 1.68-8.61), but higher hemoglobin levels were linked to neonatal asphyxia (OR 2.05, 95% CI 1.11-3.78) and higher NICU hospitalization. The other severe cohort of PE (Li et al., 2025) found independent predictive factors in risk of composite adverse pregnancy outcomes: twin pregnancy (aOR 5.59, 95% CI 2.77-11.25), increased total cholesterol (aOR 1.56, 95% CI 1.32-1.85), increased gestational age and increased placental growth factor concentrations.

The study in the United Kingdom conducted by Bramham et al. (2011) on women who had a history of early-onset PE found that systolic blood pressure more than 130 mmHg at booking and continuing proteinuria were predictors of recurring PE and recurring preterm delivery. In their Swedish study, Ulfsdottir et al. (2023) found that PE was significantly linked with more risks of SGA, neonatal compromise (e.g., resuscitation), and a small-yet-significant rise in perinatal death. In Ethiopia, the severity comparison (Jikomo et al., 2022) and the United States (Ton et al., 2020) also indicated poorer perinatal outcomes in severe PE than in the non-severe/mild PE.

Lastly, Bossung et al. (2020) found in a German cohort of very-low-birth-weight infants that preterm birth was less frequently related to intracerebral hemorrhage, necrotizing enterocolitis with the need of surgery, periventricular leukomalacia, and neonatal death than other causes of preterm birth.

Bilano et al. (2014) and Abalos et al. (2014) reported severe maternal outcomes in two WHO multicountry analyses. Pregnancy hypertensive disorders were linked to significantly high odds ratios of maternal near miss and/or maternal mortality in comparison to non-hypertensive disorder pregnancies with the greatest odds ratios being found in women with eclampsia.

Meta-analysis of perinatal outcomes

Perinatal death or stillbirth

Four studies compared the risk of perinatal death or stillbirth between pregnancies complicated by preeclampsia (PE) and normotensive pregnancies. As shown in (Figure 2) the random-effects meta-analysis, PE was associated with a significantly increased risk of perinatal death (RR 1.28, 95% CI 1.10–1.48), with no evidence of statistical heterogeneity (I^2 = 0%). The registry-based study evaluating prior PE contributed the greatest weight to the pooled estimate; however, sensitivity analysis excluding this study (Figure 3, sensitivity)yielded a slightly attenuated but still

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statistically significant association (RR 1.22, 95% CI 1.03–1.45), and heterogeneity remained absent ($I^2 = 0\%$).

Figure 2. Forest plot of relative risk for perinatal death or stillbirth comparing pregnancies with PE versus pregnancies without PE.

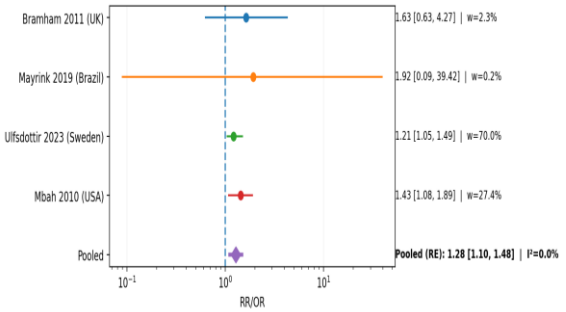
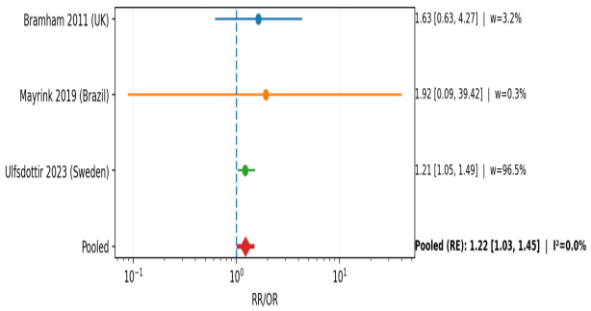


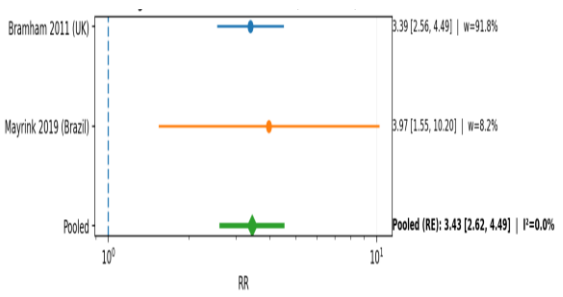
Figure 3 (sensitivity). Forest plot excluding the prior-PE registry study; the pooled estimate remains elevated with no heterogeneity.



Preterm birth < 34 weeks

Two studies (Bramham 2011; Mayrink 2019) reported effect estimates for very preterm birth (<34 weeks). As shown in Figure 4, both studies demonstrated a strong association between PE and very preterm birth. The pooled relative risk was 3.43 (95% CI 2.62–4.49) with no observed heterogeneity ($I^2 = 0\%$).

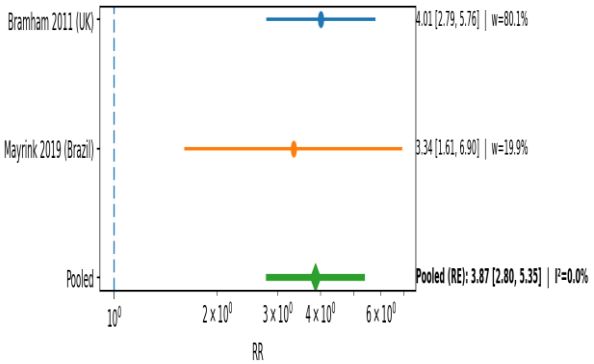
Figure 4. Forest plot of relative risk for preterm birth <34 weeks associated with PE.



NICU / neonatal unit admission

The same two studies reported neonatal intensive care unit (NICU) or special care baby unit admission. The pooled analysis (Figure 5) showed a markedly increased risk of NICU admission among infants born following pregnancies complicated by PE (RR 3.87, 95% CI 2.80–5.35), with no observed heterogeneity ($I^2 = 0\%$). Thus, infants exposed to PE in utero had an almost four-fold higher likelihood of requiring intensive neonatal care compared with those from normotensive pregnancies.

Figure 5. Forest plot of relative risk for NICU admission comparing PE versus no PE.



Severe versus non-severe preeclampsia

Two studies (Jikamo 2022; Ton 2020) compared perinatal outcomes between severe and non-severe preeclampsia. As shown in Figure 6, the pooled analysis demonstrated that severe preeclampsia was associated with a significantly higher risk of composite adverse perinatal outcomes compared with non-severe disease (RR 1.93, 95% CI 1.19–3.12). However, substantial heterogeneity was observed ($I^2 = 86.9\%$), indicating considerable variability between studies.

To explore the source of heterogeneity, a sensitivity analysis restricted to the Ethiopian cohort (Figure 7) yielded a relative risk of 1.46 (95% CI 1.38–2.77), with heterogeneity eliminated. Overall, these findings suggest that greater severity of preeclampsia is associated with increased risk of adverse perinatal outcomes, although the magnitude of effect appears to vary across settings.

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Figure 6. Forest plot comparing severe versus non-severe PE for composite adverse perinatal outcomes.

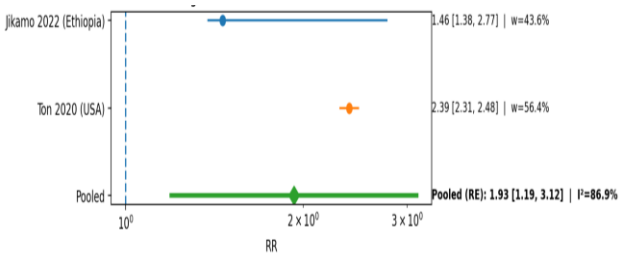
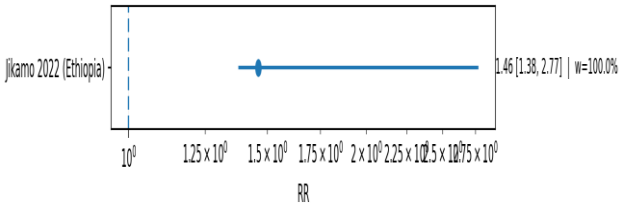


Figure 7 (sensitivity). Forest plot restricted to the Ethiopian cohort.



Assessment of publication bias

Because fewer than ten studies were available for each outcome, funnel plots were not produced. According to methodological guidance, assessment of small-study effects and publication bias is unreliable when fewer than ten studies are available, so no formal tests were conducted. A funnel plot for perinatal death was therefore not interpreted.

Discussion

Principal findings

This meta-analysis and systematic review were pooling the results of 15 observational studies that evaluated predictors of preeclampsia (PE) and its influence on perinatal outcomes in a wide range of settings. In general, PE was related to a higher risk of perinatal mortality or stillbirth, and significantly higher risks of very preterm birth (less than 34 weeks) and admission to the NICU. The results correspond to current knowledge that PE is the manifestation of dysfunction of systemic endothelium and uteroplacental dysfunction that often leads to the fetal growth restriction and early birth, which is medically necessary and triggers neonatal morbidity and mortality (Magee et al., 2022; Steegers et al., 2010).

Interpretation regarding processes and literature available.

The fact that the perinatal death/stillbirth is more common in PE-complicated pregnancies is biologically plausible. PE particularly early-onset disease is in most cases based on the abnormal placentation and disruption of spiral artery remodelling, which causes placental ischemia, oxidative stress, and the transition to antiangiogenic signalling, which contributes to fetal compromise (Steegers et al., 2010). The existing international recommendations acknowledge that PE can manifest itself with uteroplacental dysfunction (e.g., fetal growth restriction) without proteinuria, validating why the risks of perinatal outcomes are still high despite the current clinical practices (Magee et al., 2022).

Very preterm birth (less than 34 weeks) and NICU admission showed the strongest pooled associations, and this is consistent with clinical practice. PE is ultimately treated with delivery, and disease severity or an early onset of disease usually justifies IGO of preterm birth to safeguard maternal health, which raises the use of neonatal intensive care (Magee et al., 2022; Steegers et al., 2010). The existing literature also highlights that PE is one of the main causes of preventable maternal and neonatal morbidity and mortality, and it is one of the major global health issues (Duley, 2009; Steegers et al., 2010).

PE severity and inter-setting variability.

The comparison of severe and non-severe PE implied that there were greater risks of composite adverse perinatal outcomes in case of severe disease, but heterogeneity was high. This inconsistency probably indicates variation in (i) the definitions and cut-offs of cases of (severe) PE, (ii) the underlying risk of the population and comorbidity, and (iii) disparities in referral and access to neonatal intensive care. This heterogeneity has been broadly acknowledged in prognostic studies of PE, in which the diversity of definitions of PE subtypes and outcomes may restrict the ability to compare and pool the results of a study (Bucher et al., 2024; Magee et al., 2022). Practically, the heterogeneity highlights the fact that the risk gradients based on severity are real but may manifest with more strength or with less strength depending on the setting, diagnostic practice, and capacity to provide care.

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Clinical implications Predictors of PE and adverse outcomes.

In the studies included, predictors of PE and/or adverse outcomes were multifactorial and consistent with the existing knowledge. ~~Unfetal~~ (Use Unfavorable instead)pregnancy and obesity were often involved, as well as nulliparity, which aligns with the large cohort syntheses, according to which maternal history and baseline factors are crucial early predictors (Bartsch et al., 2016; Magee et al., 2022). The relevance of obesity observed is especially congruent with meta-analytic evidence of an increased likelihood of PE in overweight or obese women pre-pregnancy (He et al., 2020).

Other studies also noted prognostic indicators in PE in women, which can be used to stratify risks. As an illustration, the evidence on the relationship between laboratory markers and clinical manifestations of severity (e.g., HELLP syndrome, anemia or high hemoglobin categories) aligns with the bigger focus on defining predictors of the development of progression and complications in hypertensive disorders of pregnancy (Magee et al., 2022). Biomarkers of angiogenic imbalance (e.g., PlGF-related measures) are also gaining more and more interest as informative of risk assessment and triage in PE, but standardization and external validation remain problematic (Bucher et al., 2024).

Practically, a regular consistency of baseline clinical predictors in prevention supports screening and prophylaxis measures that are guided by guidelines. Randomized trials have shown that low-dose aspirin started early in life by high-risk women can help decrease the risk of preterm PE, which supports the relevance of early identification of pregnancy risks (Rolnik et al., 2017). Hence, the overall evidence indicates that the improvement in early antenatal risk assessment and prompt referral pathways may help to decrease the maternal and perinatal complications, especially in the areas where risk is increased by the lack of prompt diagnosis and neonatal resources (Duley, 2009; Magee et al., 2022).

Putting findings, which seem counterintuitive, into context.

One of the studies carried out found that preterm birth secondary to PE/HELLP was linked to decreased odds of some neonatal morbidities and death than birth secondary to other causes of preterm birth (Bossung et al., 2020). This trend could be indicative of variations in underlying mechanisms with prematurity: spontaneous preterm labor, infection or extreme prematurity (because of some other etiologies) might carry more neonatal risks than medical-indicated preterm birth in a well supervised PE environment. This does not mean that PE is protective, it is just stating that the signal of preterm birth may alter the risk profile of the neonatal and should be considered during counselling and interpretation (Bossung et al., 2020).

Strengths and limitations

This review was able to synthesize evidence across various countries and study designs and pool quantitatively where the definitions and effect measures were sufficiently similar. The meta-analyses displayed low heterogeneity on several outcomes (perinatal death/stillbirth, very preterm birth, and NICU admission), which reinforced the belief on the pooled estimates.

Nonetheless, there are certain restrictions to be mentioned. First, most pooled data were based on a few studies, and some analyses only used two studies, which restricted the accuracy and the possibility to discuss the effect modification. Second, clinically, clinical heterogeneity could have been caused by variation in PE definitions (including severity and timing classifications) and outcome definitions across studies (Magee et al., 2022). Third, the designs varied in terms of adjustment strategies and control of confounders and some of the effect estimates were not directly comparable across the designs. Fourth, the relative reliability of formal evaluation of publication bias was not high as the number of studies with the pooled results was less than ten; thus, no funnel plot interpretation and statistical analysis (e.g., Eggers) were provided, and no small-study effects could be ruled. Lastly, predictors that were reported in PE-only cohorts did not allow pooling but had to be synthesized in a narrative fashion and may be more subjective than quantitative synthesis.

Practice and research implications.

It is clinically significant that the findings support the role of careful antenatal monitoring and early increase in care of PE women, especially those who have a risk of

premature delivery and infant complications. They also suggest the further focus on screening of early pregnancy with the help of proven clinical risk factors and the use of biomarkers where tested and available (Bartsch et al., 2016; Bucher et al., 2024; Magee et al., 2022). It can be of significant benefit in low-resource contexts where outcome disparities are already present (Duley, 2009).

Future studies should focus on: (i) harmonized definition of PE subtypes and perinatal outcomes to facilitate stronger pooling, (ii) non-underpowered studies of predictors in varieties of settings, and (iii) validated prognostic models of clinical factors with angiogenic biomarkers to have better predicting and timing of delivery (Bucher et al., 2024; Magee et al., 2022). More research should also be conducted to measure the outcomes at extended periods rather than at the immediate perinatal period, such as infant outcome and maternal cardiovascular sequela as the extension of PE has wider consequences (Steegers et al., 2010).

Conclusion

This meta-analysis and systematic review indicate that preterm birth is linked to many adverse perinatal outcomes, such as an increased risk of perinatal death or stillbirth and a greater increase in very preterm birth and neonatal intensive care unit (NICU) hospitalization. Stability and magnitude of pooled effects of very preterm birth and NICU admission indicate clinical fact of preeclampsia especially in severe or early insidious cases often requiring medical necessity of preterm birth and with other significant implication on neonatal morbidity and healthcare utilization.

In separate studies, uncovered maternal and obstetric determinants of preeclampsia like obesity, nulliparity, multifetal gestation, previous preeclampsia, and indicators of severity of the disease were recurrently related to occurrence of preeclampsia and unfavorable postpartum results. These results highlight the significance of risk stratification of early pregnancy, prophylaxis measures in accordance with guidelines, and an increased antenatal surveillance after the diagnosis of preeclampsia, especially in women with an increased risk of developing the disease or preterm birth.

As research, research findings imply that there is need of increased standardization in definitions of preeclampsia subtypes, classifications of severity and perinatal outcomes in order to enhance comparability across studies and enhance future meta-analyses. More well-designed studies of large scale in various settings are required to optimize prediction models, elucidate the severity- and time-related risks and guide interventions that would enable the reduction of preventable perinatal morbidity and mortality related to preeclampsia.

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