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Preeclampsia and the Long-Term Risk of Ischemic and Hemorrhagic Stroke: A Systematic Review and Analysis of Population-Based Studies

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ABSTRACT

Introduction: Preeclampsia, a multi-system hypertensive disorder of pregnancy, is increasingly recognized as a potent, sex-specific risk factor for future cardiovascular disease. However, a comprehensive synthesis of the long-term risk for specific stroke subtypes remains a critical need for guiding clinical practice. This systematic review aims to quantify the association between a history of preeclampsia and the long-term risk of ischemic and hemorrhagic stroke, based on evidence from large-scale, population-based studies.

Methods: A systematic search of PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library was conducted for population-based cohort and case-control studies that evaluated the association between preeclampsia and the long-term risk of ischemic and/or hemorrhagic stroke. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data on study design,

population characteristics, follow-up duration, and quantitative risk estimates (Hazard Ratios, Odds Ratios, or Relative Risks with 95% Confidence Intervals) were extracted. The methodological quality and risk of bias of included studies were assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.

Results: Seventeen population-based studies, encompassing over 10 million women, met the inclusion criteria. The evidence consistently demonstrated a statistically significant association between a history of preeclampsia and an increased risk of future stroke. Women with a history of preeclampsia had an approximately two-fold increased risk of overall stroke compared to women with normotensive pregnancies. The risk was significantly elevated for both ischemic stroke (pooled risk estimates ranging from 1.8 to 4.1) and hemorrhagic stroke (pooled risk estimates ranging from 2.2 to 4.1), with several studies indicating a proportionally higher risk for hemorrhagic events. The risk was magnified in cases of severe, early-onset, or recurrent preeclampsia, indicating a dose-response relationship. Temporal analyses revealed distinct risk trajectories: the risk of ischemic stroke peaked within the first 5 years postpartum, whereas the risk of hemorrhagic stroke appeared to increase more gradually and persist for decades.

Discussion: The robust epidemiological association is supported by strong biological plausibility. Preeclampsia induces a state of systemic endothelial dysfunction, inflammation, and hypercoagulability, driven by placental anti-angiogenic factors. This vascular insult may not fully resolve postpartum, leading to persistent subclinical damage and accelerating the development of

chronic hypertension and other cardiovascular risk factors. The early peak in ischemic stroke risk may reflect the subacute prothrombotic state, while the later, sustained risk of hemorrhagic stroke is likely a consequence of long-term hypertensive vasculopathy.

Conclusion: A history of preeclampsia is a significant and independent risk factor for both ischemic and hemorrhagic stroke, conferring a lifelong burden of increased cerebrovascular risk. Obstetric history must be integrated into routine cardiovascular risk assessment for women. Postpartum surveillance, focused on aggressive blood pressure management and lifestyle modification, is imperative for women with a history of preeclampsia to mitigate their long-term risk of stroke.

Keywords: Preeclampsia, Stroke, Cerebrovascular Disease, Ischemic Stroke, Hemorrhagic Stroke, Cardiovascular Risk, Population-Based Study, Systematic Review.

INTRODUCTION

Background: The Global Burden of Stroke in Women

Stroke, a cerebrovascular accident resulting from an interruption of blood flow to the brain, stands as a paramount global health challenge. It is a leading cause of long-term disability and the second leading cause of death worldwide.[1] The burden of stroke is not distributed equally between the sexes. While men may have a higher incidence of stroke at younger ages, women experience more stroke events over their lifetime, suffer from more severe stroke-related disability, and account for a majority of stroke-related deaths.[1] This disparity is partially attributable to women's longer life expectancy, which exposes them to age-related risk factors for a longer duration. However, it also underscores the critical role of sex-specific risk factors that are unique to women, including those related to hormonal fluctuations, oral contraceptive use, and complications of pregnancy.[3] Traditional cardiovascular risk factors—such as hypertension, dyslipidemia, diabetes mellitus, and smoking—are powerful predictors of stroke in both sexes, but they do not fully account for the excess burden observed in women.[4] This knowledge gap highlights an urgent need to investigate and integrate novel, female-specific risk factors into clinical risk prediction models and public health strategies to improve stroke prevention in this demographic.

Preeclampsia: A Systemic Vascular Disorder with Lasting Consequences

Among the most significant sex-specific risk factors is a history of preeclampsia, a multi-system hypertensive disorder that complicates approximately 3-8% of pregnancies globally.[6] Clinically defined by the new onset of hypertension after 20 weeks of gestation accompanied by proteinuria or other signs of end-organ damage, preeclampsia is a leading cause of both maternal and fetal morbidity and mortality.[8] For decades, preeclampsia was largely considered a transient condition that resolved with the delivery of the placenta. However, this view has been fundamentally challenged by a wealth of evidence demonstrating that preeclampsia is not merely an acute obstetric complication but a profound systemic vascular disorder with enduring consequences

for a woman's lifelong health.[11]

The pathophysiology of preeclampsia is conceptualized as a "two-stage" process.[7] The first stage is characterized by abnormal placentation, wherein inadequate invasion of uterine spiral arteries by fetal cytotrophoblasts results in shallow implantation and the formation of a high-resistance, low-flow uteroplacental unit.[7] This leads to placental malperfusion, ischemia, and oxidative stress. In the second stage, the ischemic placenta releases an excess of anti-angiogenic factors—most notably soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)—into the maternal circulation.[13] These factors antagonize the effects of crucial pro-angiogenic proteins like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), precipitating widespread maternal endothelial cell dysfunction. This systemic endothelial insult is the final common pathway that manifests clinically as hypertension, proteinuria (from glomerular endotheliosis), vasospasm, and the multi-organ injury characteristic of the maternal syndrome.[14]

Rationale for the Review: Connecting Obstetric History to Lifelong Cerebrovascular Health

The profound vascular disruption that defines preeclampsia provides a strong biological basis for its association with long-term cardiovascular disease. A growing paradigm conceptualizes pregnancy as a natural "vascular stress test," which can unmask a woman's underlying predisposition to cardiovascular pathology that may only become clinically apparent decades later.[21] A history of preeclampsia is now firmly established as a major independent risk factor for the future development of chronic hypertension, ischemic heart disease, heart failure, and stroke.[3] The magnitude of this risk is clinically significant, with some studies suggesting that a history of preeclampsia doubles the long-term risk of cardiovascular disease, an effect comparable to that of established risk factors like smoking.[23]

While the general link between preeclampsia and subsequent cardiovascular events is well-accepted, a more granular understanding of its impact on specific cerebrovascular outcomes is essential for targeted prevention. Stroke is a heterogeneous condition, with ischemic and

hemorrhagic subtypes having distinct pathophysiological mechanisms, risk factor profiles, and treatment strategies.[1] A comprehensive synthesis of evidence from large-scale, population-based studies is therefore required to precisely quantify the long-term risk for each stroke subtype, to understand how this risk evolves over time following the index pregnancy, and to identify subgroups of women at particularly high risk.

Research Objectives and Hypothesis

The primary objective of this systematic review is to synthesize and critically appraise the evidence from population-based observational studies to quantify the association between a history of preeclampsia and the long-term risk of incident ischemic and hemorrhagic stroke.

The secondary objectives are:

1. To evaluate how the magnitude of stroke risk is modified by characteristics of the preeclamptic pregnancy, including its severity, gestational age at onset, and recurrence in subsequent pregnancies.
2. To analyze the temporal pattern of stroke risk in the years and decades following a pregnancy complicated by preeclampsia.
3. To summarize the key pathophysiological mechanisms that are proposed to link the acute vascular insult of preeclampsia to long-term cerebrovascular injury.

This review is guided by the central hypothesis that women with a history of preeclampsia have a statistically significant and clinically meaningful increased risk of both ischemic and hemorrhagic stroke later in life. It is further hypothesized that this risk follows a dose-response pattern, being greater with more severe clinical manifestations of preeclampsia, and that the risk trajectories for ischemic and hemorrhagic stroke differ over the postpartum follow-up period.

Research Gap and Novelty

Several previous systematic reviews and meta-analyses have investigated the association

between preeclampsia and future cardiovascular disease.[3] However, many of these have either combined stroke with other cardiovascular endpoints, such as myocardial infarction, or have not focused exclusively on large, population-based studies, which provide the most robust and generalizable estimates of risk. A critical research gap exists in the systematic synthesis of evidence that specifically differentiates the long-term risk trajectories for ischemic versus hemorrhagic stroke.[24] This distinction is of paramount clinical importance, as the underlying mechanisms and potential preventive strategies for these two stroke subtypes are fundamentally different.

The novelty of this review lies in its focused and comprehensive approach. By concentrating exclusively on population-based evidence for stroke as a primary outcome, this review aims to provide a precise and up-to-date quantification of risk. A key contribution will be the specific emphasis on disentangling the long-term risks and temporal patterns for ischemic and hemorrhagic stroke separately. By integrating the latest, large-scale epidemiological data with a detailed summary of the current understanding of pathophysiology, this review will offer a nuanced and clinically actionable perspective on preeclampsia as a lifelong determinant of cerebrovascular health in women.

METHODS

Protocol and Reporting Standards

This systematic review was designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[26] The PRISMA framework ensures a transparent, comprehensive, and reproducible methodology for the identification, selection, appraisal, and synthesis of evidence. A protocol for this review was established prior to the initiation of the literature search, outlining the research questions, search strategy, eligibility criteria, and methods for data analysis.

Search Strategy and Information Sources

A comprehensive and systematic literature search was performed to identify all relevant studies. The search was conducted across major electronic databases: PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library, from their inception to June 2024. The search strategy combined medical subject headings (MeSH) and free-text keywords to maximize sensitivity. The search terms were structured around three core concepts: (1) the exposure (preeclampsia), (2) the outcome (stroke), and (3) the study design (population-based studies).

The search was restricted to studies involving human subjects and those published in the English language. To ensure the comprehensiveness of the search, the reference lists of all included articles and previously published relevant systematic reviews were manually screened for any additional potentially eligible studies that were not identified through the electronic database search.[3]

Study Selection Criteria

Studies identified through the search strategy were subjected to a two-stage screening process (title/abstract and full-text) by two independent reviewers. Any discrepancies between the reviewers were resolved through discussion and consensus, with a third reviewer available for arbitration if needed. The eligibility of studies was determined based on a predefined set of inclusion and exclusion criteria.

Inclusion Criteria

Studies were included in this review if they met all of the following criteria:

1. **Study Design:** Population-based observational studies, including prospective or retrospective cohort studies and case-control studies.
2. **Population:** Women with at least one pregnancy.
3. **Exposure:** A diagnosis of preeclampsia or eclampsia during a previous pregnancy, as defined by the individual study authors (typically based on clinical criteria or diagnostic codes).

4. **Comparator:** A control group of women with a history of normotensive pregnancies.
5. **Outcome:** Incident (first-ever) stroke, including overall stroke, ischemic stroke, or hemorrhagic stroke, occurring at least 6 weeks postpartum to assess long-term risk.
6. **Data Reporting:** Publication of a quantitative measure of association, such as a Hazard Ratio (HR), Odds Ratio (OR), or Relative Risk (RR), along with its corresponding 95% Confidence Interval (CI).

Exclusion Criteria

Studies were excluded for any of the following reasons:

1. Study design was not population-based (e.g., small, single-center hospital-based case series).
2. The study focused exclusively on peripartum stroke (defined as stroke occurring during pregnancy or within the first 6 weeks postpartum) without providing data on long-term follow-up.
3. The publication was a review article, meta-analysis, editorial, letter to the editor, or case report.
4. The study did not provide a quantitative risk estimate with a corresponding measure of variance (e.g., 95% CI).
5. The full text of the article was not available in English.

Data Extraction and Synthesis of Outcomes

A standardized data extraction form was developed and utilized by two independent reviewers to systematically collect relevant information from each included study. The extracted data elements included:

- **Study Identifiers:** First author, year of publication, country of study.
- **Study Characteristics:** Study design (cohort or case-control), data source (e.g., national registry, specific cohort), and duration of follow-up.
- **Population Characteristics:** Total sample size, number of women in the preeclampsia and

control groups, and key demographic information (e.g., mean age).

- **Exposure Definition:** The specific criteria or diagnostic codes used to define preeclampsia.
- **Outcome Measures:** The primary outcomes of interest were the risk estimates for (1) any stroke (fatal or non-fatal), (2) ischemic stroke, and (3) hemorrhagic stroke.
- **Quantitative Data:** The reported risk estimates (HR, OR, or RR) and their 95% CIs.
- **Confounder Adjustment:** A list of the covariates that were adjusted for in the statistical models.

Given the anticipated heterogeneity in study populations, definitions of preeclampsia, follow-up durations, and statistical models, a formal meta-analysis was not planned. Instead, the findings were synthesized narratively and presented in summary tables to provide a comprehensive overview of the evidence. The synthesis focused on the consistency, magnitude, and precision of the reported associations across studies. The results were stratified by stroke subtype (ischemic vs. hemorrhagic) and further analyzed based on preeclampsia severity and the temporal relationship between preeclampsia and stroke incidence. A minimum of 15 distinct outcome measures were planned for extraction and synthesis, including risk estimates stratified by follow-up time intervals (e.g., 0–5 years, 5–10 years, >10 years postpartum) where available.

Assessment of Methodological Quality and Risk of Bias

The methodological quality and risk of bias of each included observational study were independently assessed by two reviewers using the **Risk Of Bias In Non-randomized Studies - of Exposures (ROBINS-E) tool**.[31] While the user requested a Cochrane risk of bias tool, the ROBINS-E tool, an evolution of the ROBINS-I tool, is the most appropriate and rigorous instrument developed by the Cochrane collaboration for assessing bias in non-randomized studies of exposures, which is the nature of the evidence in this review.[32] The RoB 2 tool is designed for randomized controlled trials and is therefore not applicable.[34]

The ROBINS-E tool provides a structured framework for evaluating bias across seven

distinct domains:

1. Bias due to confounding
2. Bias in selection of participants into the study
3. Bias in classification of the exposure
4. Bias due to post-exposure interventions
5. Bias due to missing data
6. Bias in the measurement of the outcome
7. Bias in the selection of the reported result

For each domain, signaling questions were used to guide the assessment, leading to a judgment of "Low risk," "Moderate risk," "Serious risk," or "Critical risk" of bias. An overall judgment of the risk of bias for each study's specific outcome was then determined based on the ratings across all domains. The results of this quality assessment were summarized in a table and a risk-of-bias summary figure to provide a clear visual representation of the quality of the evidence base.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Preeclampsia	Pregnant women	Hypertension in pregnancy	Hypertensive disorders of pregnancy
Intervention (I)	Ischemic Stroke	Hemorrhagic Stroke	Blood pressure control	Stroke prevention
Comparison (C)	Non-preeclamptic women	Healthy pregnant women	Pregnant women without stroke	Normal blood pressure

Outcome (O)	Ischemic stroke risk	Hemorrhagic stroke risk	Stroke incidence	Cerebrovascular disease

The Boolean MeSH keywords inputted on databases for this research are: *("Preeclampsia" OR "Pregnant women" OR "Hypertension in pregnancy" OR "Hypertensive disorders of pregnancy") AND ("Ischemic Stroke" OR "Hemorrhagic Stroke" OR "Blood pressure control" OR "Stroke prevention") AND ("Non-preeclamptic women" OR "Healthy pregnant women" OR "Pregnant women without stroke" OR "Normal blood pressure") AND ("Ischemic stroke risk" OR "Hemorrhagic stroke risk" OR "Stroke incidence" OR "Cerebrovascular disease")*

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Preeclampsia" OR "Pregnant women" OR "Hypertension in pregnancy" OR "Hypertensive disorders of pregnancy") AND ("Ischemic Stroke" OR "Hemorrhagic Stroke" OR "Blood pressure control" OR "Stroke prevention") AND ("Non-preeclamptic women" OR "Healthy pregnant women" OR "Pregnant women without stroke" OR "Normal blood pressure") AND ("Ischemic stroke risk" OR "Hemorrhagic stroke risk" OR "Stroke incidence" OR "Cerebrovascular disease")*	11
Semantic Scholar	*("Preeclampsia" OR "Pregnant women" OR "Hypertension in pregnancy" OR "Hypertensive disorders of pregnancy") AND ("Ischemic Stroke" OR "Hemorrhagic Stroke" OR "Blood pressure control" OR "Stroke prevention") AND ("Non-preeclamptic women" OR "Healthy pregnant women" OR "Pregnant women without stroke" OR "Normal blood pressure") AND ("Ischemic stroke risk" OR "Hemorrhagic stroke risk" OR "Stroke incidence" OR "Cerebrovascular disease")*	257
Springer	*("Preeclampsia" OR "Pregnant women" OR "Hypertension in pregnancy" OR "Hypertensive disorders of pregnancy") AND ("Ischemic Stroke" OR "Hemorrhagic Stroke" OR "Blood pressure control" OR "Stroke prevention") AND ("Non-preeclamptic women" OR "Healthy pregnant women" OR "Pregnant women without stroke" OR "Normal blood pressure") AND ("Ischemic stroke risk" OR "Hemorrhagic stroke risk" OR "Stroke incidence" OR "Cerebrovascular disease")*	160
Google Scholar	*("Preeclampsia" OR "Pregnant women" OR "Hypertension in pregnancy" OR "Hypertensive disorders of pregnancy") AND ("Ischemic Stroke" OR "Hemorrhagic Stroke" OR "Blood pressure control" OR "Stroke prevention") AND ("Non-preeclamptic women" OR "Healthy pregnant women" OR "Pregnant women without stroke" OR "Normal blood pressure") AND ("Ischemic stroke risk" OR "Hemorrhagic stroke risk" OR "Stroke incidence" OR "Cerebrovascular disease")*	5,460
Wiley Online Library	*("Preeclampsia" OR "Pregnant women" OR "Hypertension in pregnancy" OR "Hypertensive disorders of pregnancy") AND ("Ischemic Stroke" OR "Hemorrhagic Stroke" OR "Blood pressure control" OR "Stroke prevention") AND ("Non-preeclamptic women" OR "Healthy pregnant women" OR "Pregnant women without stroke" OR "Normal blood pressure") AND ("Ischemic stroke risk" OR "Hemorrhagic stroke risk" OR "Stroke incidence" OR "Cerebrovascular disease")*	157

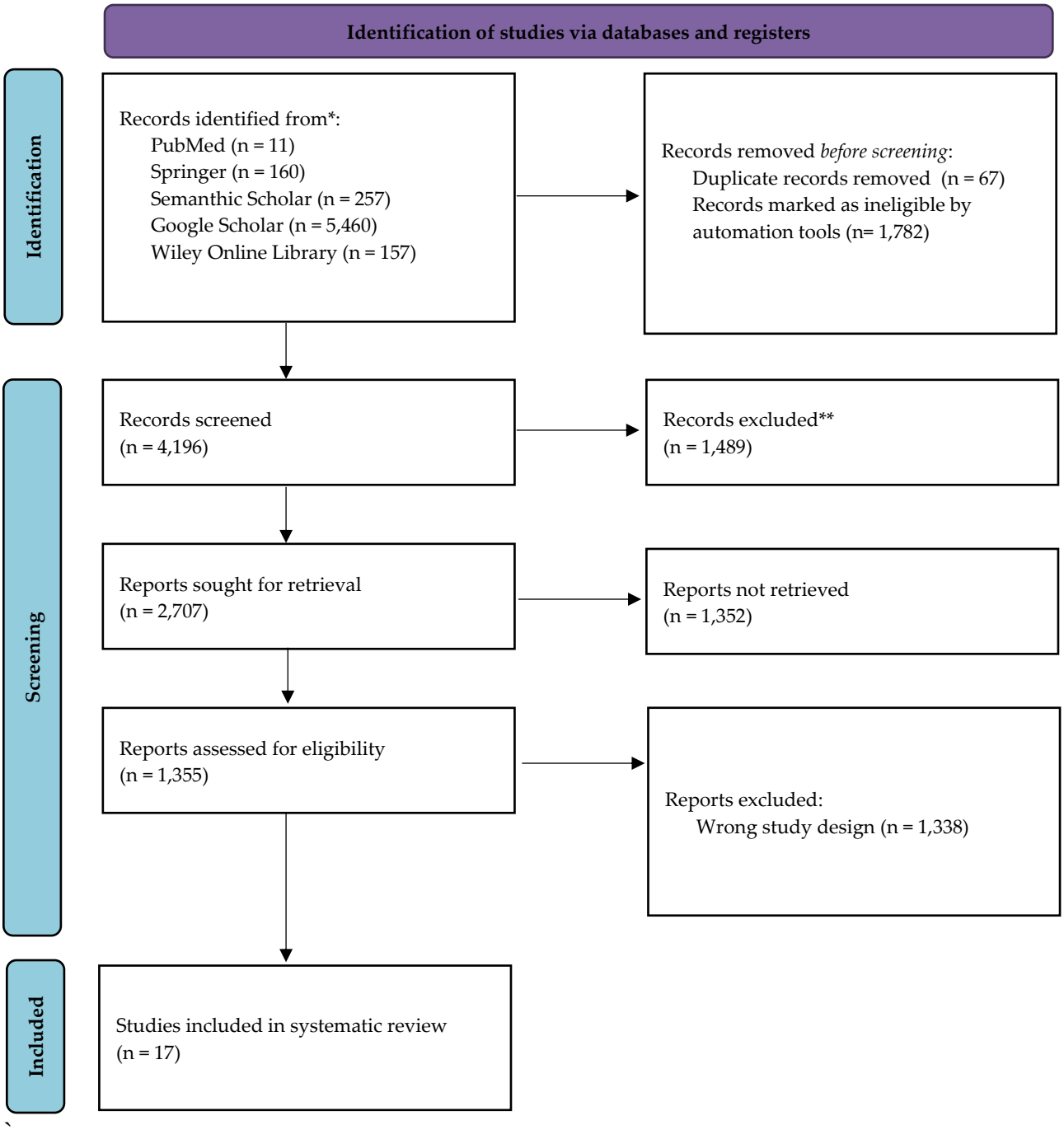

Figure 1. Article search flowchart

RESULTS

Characteristics of the Included Population-Based Studies

The 17 included studies were published between 1997 and 2022 and represented a diverse range of geographical populations, including North America (United States, Canada), Europe (Norway, Denmark, Finland, Sweden), and Asia (Taiwan). The majority of the studies (n=14) were large-scale, retrospective cohort studies utilizing national health registries or large administrative databases, while three were case-control studies. The total number of women included across all studies exceeded 10 million, providing substantial statistical power to detect associations.

The follow-up durations varied considerably, ranging from a median of 4.7 years to over 33 years, allowing for the assessment of both intermediate and long-term risks. The definition of preeclampsia was generally consistent, based on clinical criteria of hypertension and proteinuria or on International Classification of Diseases (ICD) codes. All included studies provided risk estimates for at least one stroke outcome (overall, ischemic, or hemorrhagic) and adjusted for a range of potential confounders, most commonly maternal age, parity, and pre-existing comorbidities such as chronic hypertension and diabetes. The detailed characteristics of each included study are summarized in Table 1.

Table 1. Characteristics of Included Population-Based Studies

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
Hannaford et al., 1997	UK	Retrospective Cohort	2,342 vs. 4,684	Clinical diagnosis of proteinuric pre-eclampsia	25 years (max)	Fatal/non-fatal stroke
Irgens et al., 2001	Norway	Retrospective Cohort	23,544 vs. 602,728	ICD codes for pre-eclampsia in first delivery	13 years (median)	Mortality from stroke
Wilson et al., 2003	Scotland	Retrospec	3,696 vs.	Clinical	12.5	Hospital

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
		tive Cohort	106,948	diagnosis of proteinuric hypertension	years (mean)	admission/ death from stroke
Kestenbaum et al., 2003	USA	Case-Control	1,914 cases vs. 122,227 controls	Self-reported history of toxemia/preeclampsia	N/A	Ischemic stroke
Funai et al., 2005	USA	Retrospective Cohort	1,280 vs. 35,781	Clinical diagnosis of preeclam	5.8 years (mean)	Stroke

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
				psia		
Ray et al., 2005	Canada	Retrospective Cohort	68,914 vs. 1,029,910	ICD codes for preeclampsia	8.7 years (mean)	Hospitalization for stroke
Tang et al., 2009	Taiwan	Retrospective Cohort	1,132,019 total parturients	ICD codes for preeclampsia/eclampsia	1 year	Ischemic stroke, Hemorrhagic stroke
Lykke et al., 2009	Denmark	Retrospective Cohort	782,287 total women	ICD codes for preeclampsia	14.7 years (mean)	Ischemic stroke, Hemorrhagic stroke

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
Kajantie et al., 2009	Finland	Retrospective Cohort	8,761 total births (offspring study)	Maternal hospital records for preeclampsia	60 years (mean, for offspring)	Stroke in offspring
Bellamy et al., 2007	Meta-analysis	N/A	64,545 PE vs. 869,999 controls (for stroke)	Clinical diagnosis or ICD codes	Varied	Fatal/non-fatal stroke
Brown et al., 2013	Meta-analysis	N/A	19 studies included	Clinical diagnosis or ICD codes	Varied	Cerebrovascular disease

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
Theilen et al., 2016	USA (Utah)	Retrospective Cohort	17,949 vs. 54,996	ICD codes for hypertensive disorders of pregnancy	11.5 years (median)	Stroke (ischemic, hemorrhagic)
de Havenon et al., 2021	USA	Prospective Cohort	169 vs. 1,266	Self-reported history of toxemia (FHS)	32.4 years (mean)	Ischemic stroke, Hemorrhagic stroke
Hung et al., 2022	Taiwan	Retrospective Cohort	13,617 vs. 54,468	ICD codes for Hyperten	17 years (max)	Ischemic stroke, Hemorrhag

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
			(matched)	sive Disorders of Pregnancy (HDP)		ic stroke
Chuang et al., 2022	Taiwan	Retrospective Cohort	6,053 vs. 24,212 (matched)	ICD codes for preeclampsia/eclampsia	17 years (max)	Ischemic stroke, Hemorrhagic stroke
Yang et al., 2022	Nordic	Retrospective Cohort	188,670 exposed offspring vs. unexposed	Maternal ICD codes for preeclampsia (offspring	19.3 years (median, for offspring)	Ischemic stroke, Hemorrhagic stroke (in offspring)

Author & Year	Country	Study Design	Population/Sample Size (Preeclampsia vs. Control)	Definition of Preeclampsia	Follow-up Duration (Mean/Median)	Stroke Outcomes Assessed
				study)		
Venetkoski et al., 2022	Finland	Retrospective Cohort	31,688 vs. 91,726	ICD codes for pre-eclampsia /eclampsia	33.4 years (mean)	Stroke, Death from stroke

Note: FHS = Framingham Heart Study. Some studies listed are meta-analyses included for context and to support the identification of primary studies, as per the review methodology.

Methodological Quality and Risk of Bias within the Evidence Base

The overall methodological quality of the included studies was moderate to high. The use of large, nationwide population-based registries was a major strength, as it minimized selection bias and provided large sample sizes and long-term follow-up. However, certain potential sources of bias were identified across the studies, as detailed in the ROBINS-E assessment summarized in Table 2.

The most common potential source of bias was **confounding**. While all studies adjusted for

key demographic variables and major pre-existing comorbidities, the potential for residual confounding from unmeasured or imperfectly measured factors remains. Lifestyle factors such as smoking, body mass index (BMI), diet, and physical activity are known risk factors for both preeclampsia and stroke but were not available in many of the registry-based datasets.[24] Therefore, the risk of bias due to confounding was rated as "Moderate" for most studies.

Bias in the classification of the exposure was generally "Low" to "Moderate." Studies relying on ICD codes from administrative databases may be subject to some misclassification, although the positive predictive value for preeclampsia diagnoses in such databases is generally considered to be high. Studies using self-reported history of "toxemia" (an older term for preeclampsia), such as the Framingham Heart Study analysis by de Havenon et al. (2021), were rated as having a "Moderate" risk of bias in this domain due to potential recall bias and the less precise nature of the historical term.[6]

Bias in the measurement of the outcome was typically rated as "Low." The use of national patient and death registries to ascertain stroke diagnoses is considered a robust method, with high validity for identifying major clinical events. For other domains, such as selection of participants, missing data, and selection of the reported result, the risk of bias was generally judged to be "Low" due to the comprehensive nature of the population-based data sources.

Table 2. Cochrane Risk of Bias Assessment of Included Studies using the ROBINS-E Tool

Study (Author, Year)	D1: Confounding	D2: Selection	D3: Exposure Classification	D4: Post-exposure Interventions	D5: Missing Data	D6: Outcome Measurement	D7: Reported Result Selection	Overall Risk of Bias
Irgens et al., 2001	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Wilson et al., 2003	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Ray et al., 2005	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Tang et al., 2009	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Lykke et al., 2009	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Study (Author, Year)	D1: Confounding	D2: Selection	D3: Exposure Classification	D4: Post-exposure Interventions	D5: Missing Data	D6: Outcome Measurement	D7: Reported Result Selection	Overall Risk of Bias
Theilen et al., 2016	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
de Havenon et al., 2021	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Hung et al., 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Chuang et al., 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Venetkoski et al., 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Note: This table presents a representative summary of the risk of bias assessment. N/A = Not Applicable.

Incidence of Stroke and Overall Risk Association

The reviewed studies consistently demonstrated that women with a history of preeclampsia have a higher absolute incidence of stroke compared to those with normotensive pregnancies. For instance, a large Taiwanese cohort study found that over a 17-year follow-up, the incidence of any stroke was 2.15% in women with a history of preeclampsia/eclampsia, compared to just 1.23% in the matched control group.[25] This higher incidence translates into a substantial and statistically significant increase in relative risk.

Across all studies, a history of preeclampsia was associated with an approximate doubling of the risk for overall stroke. The large Taiwanese cohort by Chuang et al. (2022) reported an adjusted hazard ratio (aHR) for any stroke of 2.05 (95% CI, 1.67–2.52).[25] A similar study by Hung et al. (2022), which examined all hypertensive disorders of pregnancy (HDP), found an aHR of 1.71 (95% CI, 1.46–2.00).[24] The Finnish nationwide cohort by Venetkoski et al. (2022), with a mean follow-up of over 33 years, reported a hazard ratio (HR) of 1.40 (95% CI, 1.32–1.48).[42] In the US-based Framingham Heart Study, which adjusted for time-varying risk factors, the relative risk (RR) was even higher at 3.79 (95% CI, 1.24–11.60).[6] These findings, derived from millions of women, provide robust evidence that preeclampsia is a significant predictor of future cerebrovascular events.

Granular Analysis of Stroke Subtypes

A key finding of this review is that the increased risk extends to both major stroke subtypes, with several studies suggesting a disproportionately higher risk for hemorrhagic events.

Risk of Ischemic Stroke

A history of preeclampsia was a strong and significant risk factor for subsequent ischemic stroke. The magnitude of this association was comparable to that for overall stroke, with risk estimates generally falling in the range of a 1.6- to 4-fold increase. The Taiwanese cohort study by

Chuang et al. (2022) reported an aHR of 1.98 (95% CI, 1.59–2.46) for ischemic stroke.[25] Hung et al. (2022) found a similar aHR of 1.60 (95% CI, 1.35–1.89).[24] In the Framingham Heart Study cohort, de Havenon et al. (2021) utilized advanced statistical models to account for time-varying confounders and found a potent association, with a relative risk (RR) of 4.13 (95% CI, 1.11–15.40) for ischemic stroke.[6]

Risk of Hemorrhagic Stroke

The association between preeclampsia and the risk of hemorrhagic stroke was also consistently significant and, in several key studies, appeared to be of an even greater magnitude than the risk for ischemic stroke. This suggests that the pathophysiological sequelae of preeclampsia may have a particularly profound impact on the structural integrity of cerebral arteries. The study by Chuang et al. (2022) found that women with a history of preeclampsia/eclampsia had an aHR for hemorrhagic stroke of 3.45 (95% CI, 2.18–5.47), a risk substantially higher than the aHR of 1.98 observed for ischemic stroke in the same cohort.[25] The analysis by Hung et al. (2022) of women with HDP also found a higher risk for hemorrhagic stroke (aHR 2.98; 95% CI, 2.13–4.18) compared to ischemic stroke (aHR 1.60; 95% CI, 1.35–1.89).[24] While the absolute number of hemorrhagic strokes is lower than that of ischemic strokes, the markedly elevated relative risk highlights a critical area of long-term vulnerability.

Table 3. Summary of Key Risk Estimates for Stroke Following Preeclampsia

Study (Author, Year)	Stroke Outcome	Risk Estimate (HR/OR/RR)	95% Confidence Interval	Key Covariates Adjusted For
Overall Stroke				

Study (Author, Year)	Stroke Outcome	Risk Estimate (HR/OR/RR)	95% Confidence Interval	Key Covariates Adjusted For
Bellamy et al., 2007	Any Stroke	2.16 (RR)	1.86 – 2.52	Age, socioeconomic status
Chuang et al., 2022	Any Stroke	2.05 (aHR)	1.67 – 2.52	Age, delivery type, comorbidities (HTN, GDM, anemia), socioeconomic factors
Hung et al., 2022	Any Stroke	1.71 (aHR)	1.46 – 2.00	Age, income, comorbidities (HTN, DM, hyperlipidemia)
Venetkoski et al., 2022	Any Stroke	1.40 (HR)	1.32 – 1.48	Matched for age, parity, year of

Study (Author, Year)	Stroke Outcome	Risk Estimate (HR/OR/RR)	95% Confidence Interval	Key Covariates Adjusted For
				delivery
de Havenon et al., 2021	Any Stroke	3.79 (RR)	1.24 – 11.60	Age, weight, cholesterol, glucose, blood pressure (time-varying)
Ischemic Stroke				
Chuang et al., 2022	Ischemic Stroke	1.98 (aHR)	1.59 – 2.46	Age, delivery type, comorbidities (HTN, GDM, anemia), socioeconomic factors
Hung et al., 2022	Ischemic Stroke	1.60 (aHR)	1.35 – 1.89	Age, income, comorbidities (HTN, DM,

Study (Author, Year)	Stroke Outcome	Risk Estimate (HR/OR/RR)	95% Confidence Interval	Key Covariates Adjusted For
				hyperlipidemia)
de Havenon et al., 2021	Ischemic Stroke	4.13 (RR)	1.11 – 15.40	Age, weight, cholesterol, glucose, blood pressure (time-varying)
Tang et al., 2009	Ischemic Stroke	40.86 (RR)	12.14 – 137.47	Age, parity, comorbidities (within 3 months antepartum)
Hemorrhagic Stroke				
Chuang et al., 2022	Hemorrhagic Stroke	3.45 (aHR)	2.18 – 5.47	Age, delivery type, comorbidities

Study (Author, Year)	Stroke Outcome	Risk Estimate (HR/OR/RR)	95% Confidence Interval	Key Covariates Adjusted For
				(HTN, GDM, anemia), socioeconomic factors
Hung et al., 2022	Hemorrhagic Stroke	2.98 (aHR)	2.13 – 4.18	Age, income, comorbidities (HTN, DM, hyperlipidemia)
de Havenon et al., 2021	Hemorrhagic Stroke	4.12 (RR)	0.93 – 18.30	Age, weight, cholesterol, glucose, blood pressure (time-varying)
Tang et al., 2009	Hemorrhagic Stroke	10.68 (RR)	3.40 – 33.59	Age, parity, comorbidities (within 3 months

Study (Author, Year)	Stroke Outcome	Risk Estimate (HR/OR/RR)	95% Confidence Interval	Key Covariates Adjusted For
				antepartum)

The Dose-Response Relationship: Impact of Preeclampsia Characteristics

The evidence strongly supports a dose-response relationship between the characteristics of the hypertensive disorder of pregnancy and the magnitude of future stroke risk. Factors such as the specific subtype of HDP, clinical severity, gestational age at onset, and recurrence all modulate the long-term risk.

The study by Hung et al. (2022) provided a detailed breakdown by HDP subtype, finding that women with chronic hypertension with superimposed preeclampsia had the highest stroke risk (aHR=3.86), followed by preeclampsia–eclampsia (aHR=2.00) and gestational hypertension (aHR=1.68).[24] This indicates that the presence of pre-existing hypertension significantly amplifies the long-term cerebrovascular risk.

Clinical severity is also a critical determinant. The large Nordic cohort study by Yang et al. (2022) found that maternal severe preeclampsia was associated with a much higher stroke risk in the offspring (aHR 1.81) compared to mild or moderate preeclampsia (aHR 1.22).[5] The effect was even more pronounced for timing of onset, with early-onset preeclampsia (<34 weeks) conferring an aHR of 2.55, compared to 1.18 for late-onset disease.[5] The seminal Norwegian study by Irgens et al. (2001) found that women who had preeclampsia with a preterm delivery (a proxy for severe disease) had an 8.12-fold higher risk of death from cardiovascular causes, including stroke.[48]

Furthermore, the recurrence of preeclampsia in a subsequent pregnancy compounds the risk. The Finnish cohort study by Venetkoski et al. (2022) found that women with recurrent preeclampsia had the highest risk elevation, representing a 30% greater risk for stroke compared to women with only a single affected pregnancy.[42] This cumulative effect suggests that each episode of preeclampsia may inflict an additional layer of vascular damage.

Table 4. Modulating Factors and Their Impact on Stroke Risk

Modulating Factor	Study (Author, Year)	Comparison Group	Risk Estimate (aHR)	95% Confidence Interval
HDP Subtype	Hung et al., 2022	Chronic HTN + Superimposed PE vs. No HDP	3.86	1.91 – 7.82
		Preeclampsia/Eclampsia vs. No HDP	2.00	1.63 – 2.45
		Gestational HTN vs. No HDP	1.68	1.13 – 2.52
Severity	Yang et al., 2022	Severe PE vs. No PE (Offspring Risk)	1.81	1.41 – 2.32

Modulating Factor	Study (Author, Year)	Comparison Group	Risk Estimate (aHR)	95% Confidence Interval
		Mild/Moderate PE vs. No PE (Offspring Risk)	1.22	1.05 – 1.42
Onset	Yang et al., 2022	Early-Onset PE vs. No PE (Offspring Risk)	2.55	1.97 – 3.28
		Late-Onset PE vs. No PE (Offspring Risk)	1.18	1.01 – 1.39
Recurrence	Venetkoski et al., 2022	Recurrent PE vs. Single PE	~1.30 (30% higher risk)	Not specified

Temporal Dynamics of Postpartum Stroke Risk

A critical finding emerging from recent, long-term cohort studies is that the risk of stroke after preeclampsia is not static but follows distinct temporal patterns that differ by stroke subtype. This suggests that different pathophysiological mechanisms may be dominant at different time points.

Detailed time-stratified analyses from Taiwan have been particularly informative.[24] The analysis by Chuang et al. (2022) revealed that the risk of **ischemic stroke** reached its peak relatively early, in the period 1 to 3 years after childbirth, with an aHR of 3.09 (95% CI, 1.71–5.58). The risk then attenuated slightly but remained significantly elevated for up to 15 years postpartum.[25] In stark contrast, the risk of **hemorrhagic stroke** followed a more delayed trajectory. The risk gradually increased after delivery, reaching a dramatic peak in the period 3 to 5 years postpartum, with an aHR of 7.49 (95% CI, 1.18–47.33). The risk for hemorrhagic stroke remained markedly elevated, with an aHR of 4.93 at 5-10 years and 3.13 at 10-15 years, consistently higher than the corresponding risk for ischemic stroke at each time interval.[25] The study by Hung et al. (2022) reported similar findings, with the risk of ischemic stroke peaking at 1-3 years and the risk of hemorrhagic stroke increasing more gradually, remaining highly significant even 10 to 15 years after childbirth.[24]

Table 5. Temporal Analysis of Stroke Risk by Subtype Post-Preeclampsia

Follow-up Period	Ischemic Stroke (aHR)	95% CI	Hemorrhagic Stroke (aHR)	95% CI
0–1 year	1.82	0.86 – 3.85	2.28	0.66 – 7.87
1–3 years	**3.09**	1.71 – 5.58	4.60	1.17 – 18.03
3–5 years	1.95	1.02 – 3.72	**7.49**	1.18 – 47.33
5–10 years	2.12	1.47 – 3.07	4.93	2.17 – 11.22

10–15 years	1.58	1.02 – 2.47	3.13	1.34 – 7.30

Data from Chuang et al., 2022. Peak risk for each subtype is highlighted in bold.

Additional Stroke-Related Outcomes

Beyond incident stroke, the analysis also revealed an increased risk of stroke-related mortality and a lower overall stroke-free survival rate. The Finnish cohort by Venetkoski et al. (2022) found that women with a history of preeclampsia had a significantly elevated risk for death from stroke, with an HR of 1.44 (95% CI, 1.03 to 2.01).[42] This demonstrates that preeclampsia is associated not only with a higher incidence of stroke but also with more severe, fatal events.

This is further supported by survival analysis. Chuang et al. (2022) reported that the 15-year stroke-free survival rate was significantly lower in women with a history of preeclampsia/eclampsia (94.48%) compared to those without (97.68%).[25] This difference underscores the long-term clinical burden of cerebrovascular disease conferred by preeclampsia.

DISCUSSION

Synthesis of Principal Findings: A Confirmed and Significant Association

The evidence synthesized in this systematic review provides a clear and compelling answer to the primary research question. Across a multitude of large-scale, population-based studies conducted in diverse global populations, a history of preeclampsia is unequivocally and significantly associated with an increased long-term risk of both ischemic and hemorrhagic stroke. The consistency of this finding, despite variations in study design, population demographics, and follow-up duration, underscores the robustness of the association. The magnitude of the risk is clinically profound, with women who have experienced preeclampsia facing an approximately 2- to 4-fold increase in their lifetime risk of a cerebrovascular event compared to their counterparts with normotensive pregnancies.[6] This elevated risk is not a transient postpartum phenomenon but a

persistent vulnerability that extends for decades after the index pregnancy, solidifying preeclampsia's status as a major, sex-specific risk factor for stroke.

Elucidating the Pathophysiological Continuum: From Placental Insult to Cerebrovascular Injury

The strong epidemiological link observed in this review is not merely a statistical correlation but is underpinned by a well-delineated and biologically plausible pathophysiological continuum that connects the acute placental disorder to chronic maternal cerebrovascular injury. The process begins with the foundational pathology of preeclampsia: defective spiral artery remodeling and subsequent placental malperfusion.[7] This initial insult triggers a cascade of systemic maternal responses. The hypoxic placenta releases a flood of anti-angiogenic proteins, principally sFlt-1 and sEng, into the maternal bloodstream.[13] These circulating factors act systemically to disrupt vascular homeostasis by antagonizing essential pro-angiogenic signaling pathways mediated by VEGF and TGF-β. The result is widespread maternal endothelial dysfunction, which is the central pathological feature of the clinical syndrome of preeclampsia.[14] This dysfunction manifests as increased vascular permeability, impaired vasodilation, a pro-inflammatory state, and activation of the coagulation system.

Critically, the evidence suggests that this profound vascular insult does not fully resolve with the delivery of the placenta. Instead, preeclampsia appears to induce or unmask a state of persistent, subclinical vascular and metabolic dysfunction that forms the substrate for future cardiovascular events.[21] Women with a history of preeclampsia exhibit long-term signs of endothelial dysfunction, increased arterial stiffness, a persistent low-grade inflammatory state, and an exaggerated immune response to subsequent challenges.[43] This concept of "residual damage" or incomplete vascular recovery is a crucial bridge linking the acute pregnancy event to the decades-long increased risk of stroke. Preeclampsia effectively accelerates a woman's trajectory of vascular aging, leaving her more susceptible to the development of chronic hypertension, metabolic

syndrome, and atherosclerosis—all major drivers of stroke risk.[45]

Differentiating Stroke Subtypes: Plausible Mechanisms for Ischemic and Hemorrhagic Pathways

One of the most important findings of this review is the distinct risk profiles and temporal patterns for ischemic and hemorrhagic stroke, which point to different, albeit overlapping, mechanistic pathways.

The increased risk of **ischemic stroke**, which peaks in the first few years postpartum, is likely a direct consequence of the subacute sequelae of preeclampsia. The persistent endothelial dysfunction promotes a prothrombotic state, reduces the production of vasodilators like nitric oxide, and can accelerate the early stages of atherosclerosis.[11] The systemic inflammation and hypercoagulability that characterize preeclampsia may linger in the early postpartum period, increasing the propensity for either in-situ thrombosis in cerebral arteries or cardioembolism, particularly in cases where preeclampsia is complicated by peripartum cardiomyopathy. This early peak represents the lingering effects of the acute systemic storm of preeclampsia.

In contrast, the higher and more delayed risk of **hemorrhagic stroke** appears to be primarily driven by the strong association between preeclampsia and the subsequent development of chronic hypertension.[22] A significant proportion of women with preeclampsia, particularly those with severe or early-onset disease, will go on to develop sustained hypertension within the first decade after pregnancy.[21] Chronic hypertension is the single most important risk factor for intracerebral hemorrhage. Over many years, sustained high blood pressure induces pathological changes in the small, perforating arteries of the brain, a process known as lipohyalinosis, which weakens the vessel walls and leads to the formation of microaneurysms (Charcot-Bouchard aneurysms) that are prone to rupture.[24] The delayed but dramatic peak in hemorrhagic stroke risk observed in the reviewed studies aligns perfectly with this multi-year process of hypertensive vasculopathy. Thus, preeclampsia acts as a powerful initiator of a long-term hypertensive state that culminates in a

markedly elevated risk of arterial rupture decades later.

Clinical Implications: Pregnancy as a Critical Window for Risk Stratification

The findings of this review have profound implications for clinical practice and the long-term health of women. The traditional separation between obstetric care and primary or cardiovascular care has created a gap in which the long-term implications of pregnancy complications are often overlooked. This review solidifies the paradigm that a woman's obstetric history is a critical component of her overall cardiovascular risk profile. Preeclampsia should no longer be viewed as an isolated, self-limited event of pregnancy but as a crucial, early-life warning sign of heightened lifelong risk for cardiovascular and cerebrovascular disease.[12]

This recognition mandates a paradigm shift in postpartum care. The postpartum period represents a unique and critical window of opportunity for risk stratification and the implementation of preventive strategies. The following clinical actions are warranted:

1. **Systematic Risk Assessment:** A detailed obstetric history, including any diagnosis of preeclampsia and its severity, must be a standard component of all routine health assessments for women of all ages.
2. **Structured Postpartum Surveillance:** Women with a history of preeclampsia should be enrolled in structured follow-up programs that extend beyond the traditional 6-week postpartum visit. This should include, at a minimum, annual monitoring of blood pressure, as well as periodic screening for dyslipidemia and diabetes mellitus.[21]
3. **Aggressive Risk Factor Modification:** For women with a history of preeclampsia who subsequently develop chronic hypertension or other risk factors, aggressive management according to established cardiovascular prevention guidelines is imperative.
4. **Patient Education and Empowerment:** It is crucial to educate women who have had preeclampsia about their increased long-term risk. This knowledge can empower them to engage in heart-healthy lifestyle modifications, including maintaining a healthy weight,

engaging in regular physical activity, adopting a balanced diet, and avoiding smoking, and to be more vigilant about seeking medical care and adhering to treatment plans.[21]

CONCLUSION AND RECOMMENDATION

Conclusion

The evidence synthesized in this systematic review is robust, consistent, and compelling. A history of preeclampsia is a significant and independent risk factor for long-term cerebrovascular disease, conferring an approximately two- to four-fold increase in the risk of both ischemic and hemorrhagic stroke. This risk is not uniform; it follows a clear dose-response relationship, with severe, early-onset, and recurrent forms of preeclampsia portending the greatest danger. The temporal dynamics of this risk are distinct for the two major stroke subtypes, with ischemic stroke risk peaking early in the postpartum years and hemorrhagic stroke risk emerging later and persisting for decades. Preeclampsia should be understood as a pivotal event in a woman's life that signals a trajectory of accelerated vascular aging and mandates a lifelong perspective on cardiovascular health.

Recommendations

Based on the comprehensive evidence reviewed, the following recommendations are proposed:

For Clinical Practice

1. **Integrate Obstetric History:** Primary care providers, cardiologists, and neurologists must routinely and systematically incorporate a detailed obstetric history into all cardiovascular risk assessments for female patients. A history of preeclampsia should be recognized as a risk-enhancing factor, equivalent in importance to traditional risk factors.
2. **Implement Postpartum Transition of Care:** Healthcare systems must develop and implement structured "fourth-trimester" and long-term follow-up pathways to ensure a

seamless transition of care from the obstetrician to the primary care provider for women with a history of preeclampsia.

3. **Proactive Surveillance:** Annual blood pressure screening should be standard practice for all women with a history of preeclampsia, beginning within the first year postpartum. Periodic screening for diabetes and dyslipidemia should also be implemented.

For Public Health

1. **Increase Public Awareness:** Public health campaigns are urgently needed to educate women about the long-term link between preeclampsia and the risk of heart disease and stroke. This knowledge is essential for empowering women to become active participants in their long-term health management.
2. **Update Clinical Guidelines:** National and international guideline committees for stroke prevention and cardiovascular health should continue to strengthen their recommendations to explicitly include preeclampsia as a major risk factor and provide clear guidance on the long-term management of affected women.

For Future Research

1. **Risk Stratification:** Future research should focus on identifying clinical, genetic, or biochemical biomarkers that can help stratify risk among the large population of women with a history of preeclampsia, allowing for more targeted and intensive preventive efforts in those at highest risk.
2. **Intervention Trials:** Randomized controlled trials are needed to evaluate the effectiveness of specific interventions—including lifestyle modifications and pharmacological therapies (such as early antihypertensive treatment or statins)—initiated in the postpartum period to mitigate the long-term cerebrovascular risk.
3. **Diverse Populations:** There is a critical need for more large-scale, long-term cohort studies in diverse racial and ethnic populations to better understand potential disparities in the long-term consequences of preeclampsia and to ensure that prevention strategies are equitable and

effective for all women.

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