PRISMA 2020 Checklist

Manuscript: The Timing of Aspirin Administration in Pregnancy (Morning vs. Bedtime) for the Prevention of Preeclampsia: A Systematic Review and Meta-Analysis

Author: Habtamu Fekadu Andeta, MD | Worabe Comprehensive & Specialized Hospital

Section & Topic	Item #	PRISMA 2020 Checklist Item Description	Location in Manuscript
TITLE	1	**The Timing of Aspirin Administration in Pregnancy (Morning vs. Bedtime) for the Prevention of Preeclampsia: A Systematic Review and Meta-Analysis**	Title Page & Main Title (Page 1)
ABSTRACT	2	Abstract Background: Low-dose aspirin is widely used to reduce the risk of preeclampsia in pregnant women at increased risk. However, whether the time of aspirin administration, particularly morning versus bedtime, influences its preventive effectiveness remains uncertain. Clarifying the evidence may help optimize aspirin administration during pregnancy. Objective: To evaluate whether morning versus bedtime administration of low-dose aspirin during pregnancy differs in its effectiveness for preventing preeclampsia. Methods: A systematic review and, if supported by the available evidence, meta-analysis will be conducted in accordance with PRISMA 2020 guidance. Electronic databases and clinical trial registries will be searched for randomized controlled trials and other eligible comparative	Abstract Section (Page 2

		studies evaluating morning versus bedtime administration of low-dose aspirin during pregnancy. The primary outcome will be preeclampsia. Secondary outcomes may include preterm preeclampsia, preterm birth, fetal growth restriction, and maternal and perinatal adverse outcomes, where reported. Study selection and data extraction will be conducted using predefined eligibility criteria. Risk of bias will be assessed using an appropriate validated tool. Where sufficient clinically comparable data are available, effect estimates will be pooled using appropriate meta-analytic methods; otherwise, findings will be synthesized narratively. Results: The number of eligible studies, participant characteristics, risk-of-bias assessments, and comparative effect estimates remain to be established through verification of the search results and extraction data. No pooled effect estimate is reported at this stage. Conclusion: The comparative effectiveness of morning versus bedtime administration of low-dose aspirin for preventing preeclampsia requires evaluation using verified, directly comparable evidence. The findings of this review may help clarify whether administration timing should influence clinical recommendations or future research. Keywords: Aspirin; preeclampsia; pregnancy; administration timing; bedtime dosing; morning dosing; systematic review; meta-analysis.	
INTRODUCTION	3	Preeclampsia is a major cause of maternal and perinatal morbidity and mortality worldwide, particularly in settings where access to antenatal surveillance, timely diagnosis, and emergency obstetric care is limited. The condition is characterized by new-onset hypertension after 20 weeks of gestation, frequently accompanied by proteinuria, maternal organ dysfunction, or uteroplacental dysfunction. Its consequences may include eclampsia, stroke, placental abruption, fetal	Section 1: Background (Pages 6)

growth restriction, medically indicated preterm birth, and maternal or perinatal death. Despite advances in antenatal care, preventing preeclampsia remains an important public health priority. Identifying effective, affordable, and practical preventive interventions is therefore essential to improving pregnancy outcomes.

Low-dose aspirin is an established preventive intervention for pregnant women at increased risk of preeclampsia. Its proposed mechanisms include inhibition of platelet thromboxane A_2 production, modification of the balance between thromboxane and prostacyclin, and effects on placental and vascular function. Evidence from randomized controlled trials and systematic reviews supports the use of low-dose aspirin to reduce the risk of preeclampsia and some associated adverse pregnancy outcomes, particularly when prophylaxis is initiated early in pregnancy. Consequently, clinical guidelines recommend low-dose aspirin for eligible women, although recommendations differ regarding the precise dose, gestational age at initiation, and timing of discontinuation. These established considerations have received considerable attention; however, the time of day at which aspirin is administered represents a distinct and potentially modifiable aspect of preventive treatment.

The biological rationale for investigating aspirin administration timing is partly based on circadian variation in blood pressure, platelet activity, vascular function, and the physiological processes implicated in preeclampsia. These processes vary throughout the day and night, potentially influencing the pharmacodynamic response to medications. Chronotherapy, which involves coordinating medication administration with biological rhythms, has therefore been proposed as a strategy for optimizing therapeutic effectiveness. In pregnancy, this concept has generated interest in whether administering low-dose aspirin at bedtime rather than in the morning could provide greater protection against preeclampsia. Nevertheless, a

plausible biological mechanism does not necessarily establish a clinically meaningful difference, and the effects of administration timing must be evaluated using comparative clinical evidence.

Previous investigations have examined the relationship between aspirin administration time and blood pressure-related outcomes, including studies suggesting that evening or bedtime administration may produce more favorable effects than morning dosing. However, findings from individual studies require careful interpretation because differences in study populations, aspirin doses, gestational age at treatment initiation, adherence, outcome definitions, and study design may influence the observed results. In addition, findings concerning blood pressure reduction cannot automatically be interpreted as evidence of reduced preeclampsia incidence. The distinction between physiological or surrogate outcomes and clinically diagnosed preeclampsia is particularly important when determining whether a specific administration schedule should be recommended in routine antenatal care.

The timing of aspirin administration is a potentially simple and inexpensive intervention because changing the time of dosing generally does not require additional medication or specialized equipment. If bedtime administration provides a clinically meaningful benefit over morning administration, this strategy could be incorporated into antenatal counseling without substantially increasing treatment costs. Conversely, if the available evidence does not demonstrate a reliable difference, women and clinicians could prioritize adherence, tolerability, and compatibility with daily routines rather than assuming that one administration time is superior. Establishing the comparative effectiveness of morning and bedtime dosing is therefore relevant not only to clinical decision-making but also to the development of clear and evidence-based preventive recommendations.

Despite the established role of low-dose aspirin in preeclampsia prevention, the evidence specifically comparing morning with bedtime administration requires focused evaluation. A review addressing this question must distinguish direct comparisons of administration timing from studies comparing aspirin with placebo or no treatment, studies evaluating different aspirin doses, and studies examining the gestational age at which prophylaxis begins. These comparisons address different clinical questions and should not be combined as though they estimate the same treatment effect. Furthermore, reports arising from the same underlying trial population must be identified to avoid double-counting participants and overstating the available evidence. Whether the directly relevant studies provide sufficient independent and comparable outcome data for quantitative synthesis must be established before a pooled estimate can be justified.

Therefore, this systematic review aims to evaluate whether morning versus bedtime administration of low-dose aspirin during pregnancy differs in its effectiveness for preventing preeclampsia. The primary objective is to compare the incidence of preeclampsia between the two administration schedules. Secondary objectives are to examine other reported maternal and perinatal outcomes, assess the methodological quality and risk of bias of eligible studies, and evaluate the consistency and certainty of the available evidence. Where sufficient independent studies with clinically comparable outcomes and extractable data are identified, a meta-analysis will be undertaken; otherwise, the findings will be synthesized narratively. By focusing specifically on administration timing, this review seeks to clarify the evidence supporting alternative aspirin dosing schedules and identify remaining uncertainties relevant to clinical practice and future research.

4 4. Objectives

Section 1: Background (Page 2)

Primary objective: To determine whether morning

		versus bedtime administration of low-dose aspirin during pregnancy differs in its effectiveness for preventing preeclampsia among pregnant women receiving aspirin prophylaxis. Secondary objectives: 1. To compare the incidence of preterm preeclampsia and other reported maternal and perinatal outcomes between morning and bedtime aspirin administration. 2. To assess the risk of bias and methodological quality of eligible studies. 3. To evaluate the consistency and certainty of the available evidence regarding the effect of aspirin administration timing. 4. To determine whether the available evidence supports quantitative synthesis and, where appropriate, estimate the comparative effect of morning versus bedtime administration on preeclampsia incidence.	
METHODS	5	5. Eligibility Criteria Study design: Randomized controlled trials and other comparative clinical studies directly evaluating morning versus bedtime administration of low-dose aspirin during pregnancy will be considered. Non-randomized studies will be eligible for the systematic review if they provide a direct comparison and sufficient information to assess potential confounding and risk of bias. Study design will be considered when determining eligibility for quantitative synthesis. Population: Pregnant women receiving low-dose aspirin for the prevention of preeclampsia, including women at increased risk because of maternal characteristics, obstetric history, or other recognized risk factors. Studies involving populations with different baseline risk profiles will be eligible if the administration-time comparison is clearly defined.	Section 2.2: Eligibility (Page 7)

Intervention: Administration of low-dose aspirin in the morning during pregnancy, at any eligible gestational age and within the dose range specified in the review protocol.

Comparator: Administration of low-dose aspirin at bedtime or in the evening during pregnancy. Studies must provide a direct comparison between the administration schedules. Studies comparing aspirin with placebo or no treatment, different aspirin doses without a direct timing comparison, or different gestational ages at treatment initiation alone will not be eligible.

Primary outcome: Incidence of preeclampsia, defined according to the diagnostic criteria used in each eligible study.

Secondary outcomes: Where reported, preterm preeclampsia, gestational hypertension, preterm birth, fetal growth restriction or small-for-gestational-age birth, placental abruption, maternal adverse events, and perinatal outcomes will be considered. Outcomes will be extracted using the definitions and follow-up periods reported by the original studies.

Publication characteristics: Studies published in any language will be considered where eligibility and outcome data can be reliably assessed. No restriction based solely on publication year will be applied. Full-text articles, trial registry records, and relevant supplementary materials will be examined to establish study eligibility and obtain outcome data. Duplicate publications and multiple reports of the same underlying study will be linked and treated as a single study.

Exclusion criteria: Studies will be excluded if they do not directly compare morning with bedtime or evening aspirin administration; do not involve pregnant women receiving aspirin prophylaxis;

	investigate aspirin treatment for an unrelated indication without relevant preeclampsia-prevention outcomes; are animal or laboratory studies; or lack sufficient information to establish eligibility. Editorials, narrative reviews, commentaries, and other publications without original comparative data will not be included as primary studies, although their reference lists may be examined to identify additional eligible reports. Protocol-only publications without outcome results will not contribute to effect estimates. Grouping of studies for synthesis: Eligible studies will initially be grouped according to the direct administration-time comparison: morning versus bedtime, with evening administration considered separately where the study schedule does not correspond to bedtime. The primary synthesis will focus on the incidence of preeclampsia. Secondary syntheses may be organized by outcome, aspirin dose, gestational age at initiation, baseline preeclampsia risk, study design, and diagnostic definition, provided that sufficient studies and data are available. Randomized and non-randomized studies will be analyzed separately where appropriate. Quantitative pooling will be undertaken only when studies provide sufficiently comparable populations, interventions, comparators, outcome definitions, and extractable data. Studies that are clinically or methodologically incompatible will be summarized narratively rather than combined statistically.	
6	6. Information Sources	Section 2.1: Information Sources (Page 2)
	A comprehensive literature search will be conducted to identify studies evaluating morning versus bedtime administration of low-dose aspirin for the prevention of preeclampsia during pregnancy. The following electronic bibliographic databases will be searched from their inception to the final search date: MEDLINE (via PubMed), Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL).	

	Clinical trial registries, including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), will be searched to identify ongoing, completed, or unpublished studies. Additional sources will include Google Scholar, the reference lists of eligible studies, and relevant systematic reviews to identify potentially eligible reports not retrieved through the database searches. Where necessary, trial registry entries, supplementary materials, and related publications will be consulted to clarify study eligibility, identify multiple reports from the same study, and obtain information on aspirin administration schedules and preeclampsia outcomes. The date of the last search will be recorded separately for each database, registry, and additional source. All sources searched, search dates, and any access limitations will be documented to support transparency and reproducibility.	
7	("Aspirin"[Mesh] OR aspirin[tiab] OR acetylsalicylic[tiab] OR "acetyl salicylic acid"[tiab] OR "low-dose aspirin"[tiab]) AND ("Pre-Eclampsia"[Mesh] OR preeclampsia[tiab] OR pre-eclampsia[tiab] OR "hypertensive disorders of pregnancy"[tiab] OR "pregnancy induced hypertension"[tiab]) AND (morning[tiab] OR bedtime[tiab] OR "bed time"[tiab] OR evening[tiab] OR night[tiab] OR nighttime[tiab] OR "time of administration"[tiab] OR chronotherapy[tiab] OR chronobiology[tiab] OR "time of dosing"[tiab])	Section 2.1: Search Strategy (Page 2)
8	8. Study Selection Process All records identified through the electronic database searches, clinical trial registries, and supplementary searching will be imported into reference-management software, and duplicate	Section 2.1–2.2: Study Selection (Page 2)

records will be removed before screening. Study selection will be conducted in two stages. First, titles and abstracts will be screened against the predefined eligibility criteria. Second, the full texts of potentially eligible reports will be retrieved and assessed to determine final inclusion.

Two reviewers will independently screen titles and abstracts and independently assess the full texts of potentially eligible reports. Disagreements will be resolved through discussion and, when necessary, consultation with a third reviewer. The reasons for exclusion at the full-text stage will be documented, and the selection process will be summarized using a PRISMA 2020 flow diagram.

Studies will be considered eligible only if they evaluate low-dose aspirin administration during pregnancy and provide a direct comparison between morning and bedtime or evening administration, with relevant data on preeclampsia prevention or other prespecified maternal or perinatal outcomes. Studies comparing aspirin with placebo, different aspirin doses without a direct administration-time comparison, or different gestational ages at treatment initiation alone will be excluded.

Multiple reports arising from the same underlying study will be linked and assessed together to prevent double-counting participants. When eligibility cannot be determined from the available report, supplementary publications, trial registry records, or additional information from study authors will be consulted where feasible. Any unresolved eligibility uncertainty will be documented.

No machine-learning or automated screening tool will be used unless its use is explicitly documented in the final review methods.

9	9. Data Collection Process	Section 2.2 & Study Protocol (Page 2)	
	A standardized data extraction form will be		

developed and piloted before data collection. Data will be extracted from the full texts of eligible reports, supplementary materials, and clinical trial registry records, where available. The extraction form will capture study identification details, study design, setting, recruitment period, participant characteristics, sample size, aspirin dose, gestational age at treatment initiation, timing of administration, treatment duration, adherence, outcome definitions, follow-up periods, and reported results.

For the primary outcome, the number of participants developing preeclampsia and the total number of participants in each administration-time group will be extracted whenever available. Secondary outcome data will be collected according to the prespecified outcomes and the definitions reported by the original investigators. Adjusted and unadjusted effect estimates, measures of uncertainty, and information required to assess risk of bias will also be recorded where applicable.

To minimize extraction errors, extracted data will be checked against the original reports. Where feasible, two reviewers will independently extract the data or one reviewer will extract the data and a second reviewer will verify the extracted information. Discrepancies will be resolved through discussion and reference to the original publication, supplementary materials, or trial registry records. If essential information is missing or unclear, study authors will be contacted where feasible.

Multiple reports from the same underlying study will be linked to obtain the most complete and accurate dataset without double-counting participants. Data will not be inferred, imputed, or reconstructed solely to increase the number of eligible studies or enable quantitative synthesis. Missing or unreported information will be recorded as not reported, and unresolved uncertainties will be documented. Only verified and sufficiently comparable data will be used in quantitative analyses; otherwise, findings will be presented

narratively.

The final review will report the data extraction procedures actually implemented, including the number of reviewers involved, whether extraction was independent or verified, and any deviations from the planned methods.

10a 10a. Outcomes Section 2.2: Outcomes (Page 2)

Primary outcome

The primary outcome will be the incidence of preeclampsia, defined as the proportion of pregnant women diagnosed with preeclampsia among those receiving low-dose aspirin in the morning compared with those receiving low-dose aspirin at bedtime. Preeclampsia will be defined according to the diagnostic criteria used in each included study, generally involving new-onset hypertension after 20 weeks of gestation accompanied by proteinuria and/or other evidence of maternal organ dysfunction or uteroplacental dysfunction. The number of participants experiencing preeclampsia and the total number of participants in each administration-time group will be extracted whenever available.

Secondary outcomes

1. Preterm preeclampsia: Preeclampsia occurring before 37 completed weeks of gestation, or according to the gestational-age threshold specified in the original study. The definition used by each study will be recorded.

2. Gestational hypertension: New-onset hypertension after 20 weeks of gestation without the additional diagnostic features required for preeclampsia, according to the criteria used in the original study.

3. Preterm birth: Delivery before 37 completed

weeks of gestation.

4. Fetal growth restriction or small-for-gestational-age birth: Fetal growth restriction diagnosed antenatally or birth weight below a specified gestational-age percentile, commonly the 10th percentile, according to the study's definition.

5. Placental abruption: Premature separation of the placenta before delivery, as diagnosed and reported by the original investigators.

6. Maternal adverse events: Any reported adverse effects associated with aspirin administration, including clinically relevant bleeding, gastrointestinal symptoms, allergic reactions, or other maternal complications.

7. Perinatal outcomes: Stillbirth, perinatal death, neonatal death, and other clinically relevant neonatal outcomes, where reported and defined by the included studies.

Additional outcomes related to administration timing

Where available, differences in maternal blood pressure, adherence to the prescribed aspirin regimen, and treatment discontinuation will also be extracted as supplementary outcomes. These measures will be analyzed separately from the primary clinical outcome because changes in blood pressure or adherence do not necessarily establish a reduction in preeclampsia incidence.

For every outcome, the review will record the operational definition, measurement method, assessment time point, and effect estimate reported by the original investigators. For dichotomous outcomes, event counts and denominators will be extracted for each administration-time group. For continuous outcomes, group-specific means,

standard deviations, and sample sizes will be collected where available.

Outcomes will be sought regardless of whether the reported results are statistically significant. When multiple definitions or assessment time points are reported, the review will follow prespecified selection rules to avoid selective outcome reporting. Outcomes not reported by an included study will be recorded as not reported rather than assumed to have occurred zero times. Quantitative synthesis will be undertaken only when the available data are sufficiently comparable and adequate for the intended analysis.

10b	10b. Other Variables	Section 2.2 & Table 1 (Pages 2–3)

In addition to the outcomes specified in Item 10a, data will be sought on study characteristics, participant characteristics, intervention details, methodological characteristics, and other variables that may influence the relationship between aspirin administration timing and the prevention of preeclampsia.

1. Study identification and publication characteristics

The following variables will be collected: first author, publication year, article title, journal, country, study setting, recruitment period, funding source, declared conflicts of interest, trial registration number, and availability of a published protocol. Multiple reports from the same underlying study will be linked using study identifiers, recruitment dates, setting, sample size, and author information to prevent duplicate inclusion of participants.

2. Study design and methodological characteristics

Data will be collected on study design, including randomized controlled trial or non-randomized comparative study; allocation method; method of

sequence generation; allocation concealment; blinding of participants, healthcare personnel, and outcome assessors; sample size; duration of follow-up; completeness of outcome data; and analysis population. For randomized trials, information relevant to the risk-of-bias assessment will be recorded according to the selected risk-of-bias tool.

3. Participant characteristics

The following variables will be sought, where available: total number of participants enrolled and analyzed; maternal age; parity; body mass index; singleton or multiple pregnancy; gestational age at recruitment; previous history of preeclampsia; chronic hypertension; pregestational or gestational diabetes; renal disease; autoimmune disease; and other recognized risk factors for preeclampsia. The criteria used to classify participants as being at increased risk will also be recorded.

4. Aspirin intervention characteristics

Intervention-related variables will include aspirin dose in milligrams per day; formulation, where reported; frequency of administration; timing of administration; operational definition of morning, evening, or bedtime dosing; gestational age at treatment initiation; planned gestational age at discontinuation; duration of treatment; and use of any co-interventions relevant to preeclampsia prevention.

5. Adherence and treatment implementation

Where reported, data will be collected on adherence to the assigned administration schedule, missed doses, treatment discontinuation, crossover between administration times, changes in prescribed dosing schedules, and the methods used to measure adherence. These variables will help assess whether the intended timing contrast was maintained

throughout the study.

6. Comparator characteristics

For each comparator group, the prescribed aspirin dose, administration schedule, treatment duration, gestational age at initiation, and relevant co-interventions will be recorded. Any differences between groups other than administration timing will be documented because they may affect the interpretation of comparative results.

7. Outcome measurement and reporting characteristics

Additional variables will include the diagnostic criteria for preeclampsia, criteria for severe or preterm preeclampsia, outcome ascertainment methods, assessment time points, duration of follow-up, and whether outcomes were prespecified in the study protocol or trial registry. The source of each extracted result, including the main publication, supplementary material, registry record, or information obtained from study authors, will be documented where applicable.

8. Missing data and additional information

The review will record missing or unclear information relevant to eligibility, study characteristics, intervention timing, outcomes, and risk of bias. Attempts to obtain additional information from trial registries, supplementary publications, or study authors will be documented. Missing information will not be inferred without adequate supporting evidence.

Use of variables in the analysis

These variables will primarily be used to describe the included studies, assess clinical and methodological comparability, evaluate risk of bias,

		and interpret the findings. Where a sufficient number of independent studies and appropriate data are available, prespecified variables such as aspirin dose, gestational age at initiation, baseline preeclampsia risk, and study design may be considered in subgroup or sensitivity analyses. Such analyses will be conducted only when methodologically justified. No variable will be used to generate unsupported estimates or to increase the number of studies eligible for quantitative synthesis.	
11	10b. Other Variables	In addition to the outcomes specified in Item 10a, data will be sought on study characteristics, participant characteristics, intervention details, methodological characteristics, and other variables that may influence the relationship between aspirin administration timing and the prevention of preeclampsia. 1. Study identification and publication characteristics The following variables will be collected: first author, publication year, article title, journal, country, study setting, recruitment period, funding source, declared conflicts of interest, trial registration number, and availability of a published protocol. Multiple reports from the same underlying study will be linked using study identifiers, recruitment dates, setting, sample size, and author information to prevent duplicate inclusion of participants. 2. Study design and methodological characteristics Data will be collected on study design, including randomized controlled trial or non-randomized comparative study; allocation method; method of sequence generation; allocation concealment; blinding of participants, healthcare personnel, and outcome assessors; sample size; duration of follow-	Section 2.3: Risk of Bias (Page 2)

up; completeness of outcome data; and analysis population. For randomized trials, information relevant to the risk-of-bias assessment will be recorded according to the selected risk-of-bias tool.

3. Participant characteristics

The following variables will be sought, where available: total number of participants enrolled and analyzed; maternal age; parity; body mass index; singleton or multiple pregnancy; gestational age at recruitment; previous history of preeclampsia; chronic hypertension; pregestational or gestational diabetes; renal disease; autoimmune disease; and other recognized risk factors for preeclampsia. The criteria used to classify participants as being at increased risk will also be recorded.

4. Aspirin intervention characteristics

Intervention-related variables will include aspirin dose in milligrams per day; formulation, where reported; frequency of administration; timing of administration; operational definition of morning, evening, or bedtime dosing; gestational age at treatment initiation; planned gestational age at discontinuation; duration of treatment; and use of any co-interventions relevant to preeclampsia prevention.

5. Adherence and treatment implementation

Where reported, data will be collected on adherence to the assigned administration schedule, missed doses, treatment discontinuation, crossover between administration times, changes in prescribed dosing schedules, and the methods used to measure adherence. These variables will help assess whether the intended timing contrast was maintained throughout the study.

6. Comparator characteristics

For each comparator group, the prescribed aspirin dose, administration schedule, treatment duration, gestational age at initiation, and relevant co-interventions will be recorded. Any differences between groups other than administration timing will be documented because they may affect the interpretation of comparative results.

7. Outcome measurement and reporting characteristics

Additional variables will include the diagnostic criteria for preeclampsia, criteria for severe or preterm preeclampsia, outcome ascertainment methods, assessment time points, duration of follow-up, and whether outcomes were prespecified in the study protocol or trial registry. The source of each extracted result, including the main publication, supplementary material, registry record, or information obtained from study authors, will be documented where applicable.

8. Missing data and additional information

The review will record missing or unclear information relevant to eligibility, study characteristics, intervention timing, outcomes, and risk of bias. Attempts to obtain additional information from trial registries, supplementary publications, or study authors will be documented. Missing information will not be inferred without adequate supporting evidence.

Use of variables in the analysis

These variables will primarily be used to describe the included studies, assess clinical and methodological comparability, evaluate risk of bias, and interpret the findings. Where a sufficient number of independent studies and appropriate data are available, prespecified variables such as aspirin dose, gestational age at initiation, baseline

preeclampsia risk, and study design may be considered in subgroup or sensitivity analyses. Such analyses will be conducted only when methodologically justified. No variable will be used to generate unsupported estimates or to increase the number of studies eligible for quantitative synthesis.

12 12. Effect Measures — Section 2.4: Statistical Synthesis (Page 2)

For the primary outcome, the incidence of preeclampsia, the risk ratio (RR) with a 95% confidence interval (CI) will be used to compare morning versus bedtime administration of low-dose aspirin. The risk ratio will represent the risk of preeclampsia in the morning-administration group relative to the bedtime-administration group. An RR below 1 will indicate a lower risk with morning administration, an RR above 1 will indicate a lower risk with bedtime administration, and an RR of 1 will indicate no difference between groups.

For dichotomous secondary outcomes, including preterm preeclampsia, gestational hypertension, preterm birth, fetal growth restriction, placental abruption, maternal adverse events, and perinatal outcomes, risk ratios with 95% confidence intervals will be used where appropriate. If eligible studies report adjusted effect estimates from non-randomized comparative studies, adjusted estimates and their 95% confidence intervals will be extracted and considered separately from unadjusted estimates when appropriate to account for potential confounding.

For continuous outcomes, including maternal blood pressure measurements, the mean difference (MD) with a 95% confidence interval will be used when studies measure the same outcome on the same scale and at comparable time points. The standardized mean difference (SMD) will be considered if studies measure the same underlying construct using different scales. The direction of each effect measure will be defined consistently so that the interpretation of results is clear.

Where studies report only alternative effect measures, such as odds ratios (ORs), hazard ratios (HRs), or regression coefficients, these estimates will be recorded with their corresponding confidence intervals and interpreted according to the outcome and study design. Conversion to another effect measure will be undertaken only when the required information and assumptions are available and the conversion is methodologically justified. Incompatible effect measures will not be combined indiscriminately.

All effect estimates will be accompanied by 95% confidence intervals. Statistical synthesis will be undertaken only when the included studies provide sufficiently comparable interventions, outcomes, and data. If quantitative pooling is not appropriate, study-specific effect estimates will be presented in tables and summarized narratively.

13a-d	13a. Eligibility Criteria for Each Synthesis	Section 2.4: Data Synthesis (Page 2)

Studies will be grouped for synthesis according to the direct comparison of morning versus bedtime administration of low-dose aspirin during pregnancy. The primary synthesis will evaluate the incidence of preeclampsia. Secondary syntheses will address the prespecified maternal and perinatal outcomes reported in eligible studies.

Before combining results, studies will be assessed for clinical and methodological comparability, including population characteristics, aspirin dose, definition of administration timing, gestational age at treatment initiation, outcome definitions, follow-up periods, and study design. Randomized and non-randomized comparative studies will be considered separately where appropriate. Studies will contribute to a quantitative synthesis only when they provide relevant, sufficiently comparable outcome data. Studies that do not meet these requirements will be included in the systematic review where eligible but summarized narratively.

Multiple publications from the same underlying study will be linked, and participants will be counted only once within each synthesis. The eligibility criteria for each synthesis will be applied consistently, regardless of the direction or statistical significance of the reported results.

13b. Data Preparation for Synthesis

Data extracted from eligible reports will be checked against the original publications, supplementary materials, and trial registry records where available. For dichotomous outcomes, the number of participants experiencing the outcome and the total number of participants in each administration-time group will be extracted. For continuous outcomes, group-specific means, standard deviations, and sample sizes will be obtained where reported.

The direction of effect measures will be standardized so that comparisons consistently represent morning administration relative to bedtime administration. Risk ratios with 95% confidence intervals will be used for dichotomous outcomes when appropriate. Mean differences will be used for continuous outcomes measured on comparable scales, while standardized mean differences may be used when the same underlying construct is measured using different scales.

Missing, unclear, or inconsistent data will be recorded and investigated using other available reports or by contacting study authors where feasible. No event counts, standard deviations, or other essential statistics will be inferred solely to enable quantitative pooling. Where data cannot be reliably obtained or reconciled, the relevant outcome will be excluded from quantitative synthesis and described narratively. Any transformations or conversions will be undertaken only when supported by the available data and methodologically justified.

13c. Methods for Tabulating and Visually Displaying Results

Study characteristics, participant characteristics, aspirin administration schedules, outcome definitions, risk-of-bias assessments, and individual study results will be summarized in structured tables. For each outcome, tables will report the study identification, administration-time groups, available sample sizes, outcome data, effect estimates, and 95% confidence intervals where available.

Where quantitative synthesis is appropriate, forest plots will be used to display study-specific effect estimates and confidence intervals alongside the pooled estimate. The number of studies and participants contributing to each synthesis will be reported. Results that cannot be combined statistically will be presented in tables and summarized narratively, with attention to the direction, magnitude, precision, and consistency of the findings. Findings from randomized and non-randomized studies will be distinguished where appropriate.

13d. Methods for Statistical Synthesis

Where at least two independent studies provide sufficiently comparable data for an outcome, quantitative synthesis will be considered. For the primary outcome of preeclampsia, the risk ratio with a 95% confidence interval will be the principal effect measure. Risk ratios will be calculated from the event counts and denominators reported for the morning and bedtime groups, where these data are available and suitable for analysis.

A random-effects meta-analysis will be considered when clinical or methodological diversity indicates that the underlying treatment effects may differ across studies. The specific estimator for between-

study variance will be selected and documented according to the number of studies, available data, and suitability of the model. A fixed-effect model may be considered as a sensitivity analysis where appropriate. Between-study heterogeneity will be assessed using the Cochran Q test and the I^2 statistic, with the estimated between-study variance reported where applicable. Heterogeneity statistics will be interpreted cautiously when few studies are available.

For continuous outcomes, mean differences or standardized mean differences will be pooled as appropriate. Separate analyses will be conducted for distinct outcomes, clinically different follow-up periods, or incompatible definitions. Adjusted estimates from non-randomized studies will not be combined indiscriminately with unadjusted estimates from randomized trials.

If the available studies are too few, the data are incompatible, or the estimates cannot be calculated reliably, no pooled effect will be reported for that outcome. In such circumstances, the evidence will be synthesized narratively, and the reasons for not conducting a meta-analysis will be documented.

All statistical analyses, software, packages, model specifications, and relevant analytical decisions will be reported transparently in the final manuscript. No pooled estimate or heterogeneity statistic will be presented as a completed result until the underlying data and calculations have been verified.

14	14. Reporting Bias Assessment	Section 2.3–2.4 (Page 2)

The potential for bias due to missing results, including publication bias and selective non-reporting of outcomes, will be assessed by comparing the findings reported in published articles with available study protocols, clinical trial registry records, and supplementary materials, where available. Particular attention will be paid to discrepancies between prespecified and reported outcomes, missing outcome data at the study-

	reporting level, and evidence that results may have been selectively reported according to their direction, magnitude, or statistical significance. Where a sufficient number of independent studies contribute to a quantitative synthesis, funnel plots may be used to explore small-study effects. If at least 10 studies are available for an outcome, a statistical test for funnel-plot asymmetry, such as Egger's regression test, may be considered when appropriate for the effect measure and data structure. Any asymmetry will be interpreted cautiously because it may reflect clinical heterogeneity, methodological differences, or chance rather than publication bias alone. If fewer than 10 studies contribute to a synthesis, formal tests for funnel-plot asymmetry will generally not be performed because their power and interpretability are limited. The absence of detected asymmetry will not be interpreted as evidence that publication bias is absent. When quantitative assessment is not feasible, potential reporting biases will be discussed qualitatively using the available trial registry records, protocols, published reports, and other relevant evidence. All assessments and limitations will be reported transparently. No statistical test for publication bias or funnel-plot analysis will be reported as completed unless it has actually been conducted and the underlying data support its use.	
15	15. Certainty Assessment The certainty of the body of evidence for the primary outcome, incidence of preeclampsia, and important secondary maternal and perinatal outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The certainty of evidence will be classified as high, moderate, low, or very low.	Section 2.3 & Discussion (Pages 2, 4)

For randomized controlled trials, the certainty of evidence will be evaluated across five domains: risk of bias, inconsistency of results, indirectness of evidence, imprecision of effect estimates, and publication bias. For non-randomized comparative studies, the appropriate GRADE approach will be applied, taking into account the potential for confounding and other limitations associated with observational evidence.

Risk of bias will be judged using the results of the prespecified study-level assessment. Inconsistency will be evaluated by considering the direction and magnitude of study-specific estimates, their confidence intervals, and statistical heterogeneity where quantitative synthesis is appropriate. Indirectness will be assessed by examining the relevance of the study populations, aspirin doses, administration schedules, outcome definitions, and follow-up periods to the review question. Imprecision will be evaluated by considering the width of confidence intervals, the number of participants and events, and whether the estimates are compatible with clinically important benefit or harm. Potential publication bias will be considered using available trial registry records, study protocols, and other relevant evidence, with statistical assessments performed only when justified by the number and characteristics of included studies.

The certainty of evidence will be assessed separately for each important outcome rather than assigning a single certainty rating to the entire review. Reasons for downgrading or, where applicable, upgrading the certainty of evidence will be documented and justified. A Summary of Findings table will present the main outcomes, comparative effect estimates, confidence intervals, number of contributing studies and participants, and corresponding GRADE certainty ratings where sufficient data are available.

If the available evidence is too limited or heterogeneous to support quantitative synthesis,

		certainty will still be assessed using the applicable GRADE principles, with explicit consideration of the limitations of the available evidence. No certainty rating will be assigned until the eligible studies and their findings have been verified.	
RESULTS	16a-b	16a. Study Selection The study selection process will be reported in accordance with the PRISMA 2020 guidelines. Records identified through electronic databases, clinical trial registries, and supplementary sources will be documented separately. After removal of duplicate records, the remaining records will be screened by title and abstract against the predefined eligibility criteria. Full texts of potentially eligible reports will then be assessed for inclusion. The numbers of records identified, duplicates removed, records screened, records excluded at title and abstract screening, full-text reports sought and assessed, and reports excluded with reasons will be recorded. The final numbers of included reports and unique underlying studies will be distinguished to avoid double-counting multiple publications from the same study. The study selection results will be presented in a PRISMA 2020 flow diagram. The final report will include the actual numbers at each stage and the reasons for full-text exclusion. 16b. Excluded Studies Full-text reports that appear potentially eligible during initial screening but do not meet the predefined inclusion criteria will be listed with explicit reasons for exclusion. Reasons may include absence of a direct morning-versus-bedtime or evening aspirin comparison, an ineligible population or intervention, lack of relevant preeclampsia-prevention outcomes, publication of a study protocol without outcome data, or insufficient information to establish eligibility.	Section 3.1: Study Selection (Page 9)

	Multiple reports of the same underlying study will be linked and evaluated together. Duplicate publications will not be counted as separate studies. Reports will be excluded only after their eligibility has been assessed against the prespecified criteria, and the reason for each full-text exclusion will be documented. The final manuscript will provide a supplementary table of important full-text reports excluded after assessment, with the corresponding reason for each exclusion. The PRISMA flow diagram and exclusion table will be completed using the verified search and screening records.	
17	17. Study Characteristics	Section 3.2 & Table 1 (Pages 2–3)
	The characteristics of all included studies will be summarized in a structured table. Each study will be cited in the text and reference list, and multiple reports from the same underlying study will be linked to avoid double-counting participants. For each included study, the following characteristics will be reported: first author and publication year; country and study setting; study design; recruitment period; sample size; participant eligibility criteria and baseline risk of preeclampsia; maternal characteristics; aspirin dose; gestational age at treatment initiation; definition of morning, evening, or bedtime administration; treatment duration; adherence assessment; comparator schedule; outcome definitions; follow-up period; and funding or conflicts of interest, where reported. The study characteristics will be presented in Table 1. Particular attention will be given to differences in aspirin dose, administration schedules, gestational age at initiation, baseline maternal risk, and diagnostic criteria for preeclampsia, because these factors may influence the comparability and interpretation of the findings.	

	Only verified information obtained from the original publications, supplementary materials, clinical trial registry records, or study authors will be reported. Information not available in the source reports will be recorded as not reported. Uncertain information will not be inferred, and overlapping publications will be identified and linked to their corresponding underlying studies. The final narrative will describe the distribution of study designs, geographical settings, participant populations, and aspirin administration schedules. It will also identify important similarities and differences between studies that may affect the interpretation or feasibility of quantitative synthesis.	
18	18. Risk of Bias in Studies The risk of bias of each included study will be assessed using a tool appropriate to its study design. For randomized controlled trials, the Cochrane Risk of Bias 2 (RoB 2) tool will be used to assess bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. If eligible non-randomized comparative studies are identified, an appropriate tool, such as ROBINS-I, will be used. Risk-of-bias judgments will be based on information reported in the publications, trial registries, protocols, and supplementary materials where available. Each domain will be judged according to the guidance for the selected tool, and an overall judgment will be assigned as appropriate. Any disagreements between assessors will be resolved through discussion and, if necessary, consultation with a third reviewer. The assessment process and number of assessors will be reported according to the procedures actually performed. The risk-of-bias results will be presented in a table showing each study's judgment for the relevant domains and its overall judgment. Supporting	Section 3.2 & Table 1 (Pages 2–3)

		explanations will be provided for judgments that materially affect interpretation of the findings. Risk-of-bias assessments will inform the interpretation of individual study results and the certainty of the evidence. No study-specific judgments will be assigned until the eligible studies and their relevant methodological information have been verified.	
19	19. Results of Individual Studies		Section 3.3 & Figure 1 (Pages 3–4)
		For each included study, the results will be presented separately for morning and bedtime aspirin administration. For dichotomous outcomes, including preeclampsia, preterm preeclampsia, gestational hypertension, preterm birth, fetal growth restriction or small-for-gestational-age birth, placental abruption, maternal adverse events, and relevant perinatal outcomes, the number of participants experiencing the outcome and the total number assessed will be reported for each group. Where reported or calculable from verified data, study-specific effect estimates, preferably risk ratios (RRs) with 95% confidence intervals (CIs), will be presented.	
		For continuous outcomes, such as systolic and diastolic blood pressure, group-specific means and standard deviations will be reported when available. Mean differences (MDs) with 95% CIs will be presented when the outcome is measured on a comparable scale. Standardized mean differences will be considered only when studies assess the same underlying construct using different scales and the data are suitable for this approach.	
		Adjusted effect estimates from non-randomized studies, if eligible, will be reported separately from randomized-trial estimates and will not be combined indiscriminately with unadjusted estimates or measures of different types. When a study does not report sufficient information to calculate an effect estimate or its confidence interval, the available results will be reported as published and the missing information will be	

	identified as not reported or unresolved, as appropriate. No event counts, standard deviations, or effect estimates will be inferred without adequate supporting data. The results will be summarized in study-level tables and, where appropriate, forest plots. All eligible outcomes will be reported regardless of the direction, magnitude, or statistical significance of the findings. If the evidence does not support a reliable effect estimate, the study findings will be presented descriptively rather than generating an unsupported estimate.	
20a-d	20a. Results of Statistical Syntheses The results of each statistical synthesis will be reported for every outcome for which the included studies provide sufficiently comparable data. For dichotomous outcomes, the pooled effect estimate will be expressed as a risk ratio (RR) with a 95% confidence interval (CI). For continuous outcomes, mean differences (MDs) with 95% CIs will be reported when studies use comparable measurement scales; standardized mean differences will be considered when different scales measure the same underlying construct. The direction of each effect estimate will be defined consistently to distinguish whether the results favor morning or bedtime aspirin administration. Study-specific estimates and pooled estimates, when appropriate, will be presented in forest plots and accompanying tables. Outcomes that cannot be quantitatively synthesized will be summarized narratively, with the reasons for not pooling clearly stated. At the current stage, the eligible evidence and extractable outcome data have not been sufficiently verified to report completed pooled estimates. No pooled effect size or statistical significance claim is therefore presented.	Section 3.3 & Figure 1 (Pages 3–4)

20b. Results of Statistical Heterogeneity

For each quantitative synthesis, statistical heterogeneity will be evaluated using Cochran's Q test, the I^2 statistic, and the between-study variance estimate (τ^2), where appropriate. The magnitude and uncertainty of heterogeneity will be considered alongside differences in study design, aspirin dose, timing definitions, gestational age at treatment initiation, participant risk profiles, outcome definitions, and follow-up periods.

The I^2 statistic will not be interpreted in isolation, and the Q test will be interpreted cautiously when few studies are available. Heterogeneity statistics will be reported only for syntheses actually conducted. Because no verified quantitative synthesis is currently available, no numerical heterogeneity estimate can be reported.

20c. Results of Investigations of Possible Causes of Heterogeneity

If sufficient studies are available, prespecified subgroup analyses or meta-regression may be considered to investigate clinically plausible sources of heterogeneity. Potential factors include aspirin dose, the operational definition of morning versus bedtime administration, gestational age at initiation, baseline preeclampsia risk, and study design.

Such analyses will be conducted only when supported by an adequate number of independent studies and sufficiently comparable data. Any exploratory analyses will be clearly distinguished from prespecified analyses. Differences between subgroup estimates will be assessed using an appropriate formal interaction test rather than by comparing statistical significance within individual subgroups.

No subgroup or meta-regression findings are

	reported at this stage because the number of eligible independent studies and the availability of relevant data remain unverified. 20d. Results of Sensitivity Analyses Where quantitative synthesis is appropriate, sensitivity analyses may be conducted to assess the robustness of the findings. These may include excluding studies at high risk of bias, restricting analyses to randomized controlled trials, examining the influence of individual studies, and comparing the primary analysis with alternative defensible statistical assumptions or estimators when sufficient data are available. Sensitivity analyses will be reported with their effect estimates, 95% CIs, and relevant heterogeneity statistics, together with an explanation of whether the conclusions differ from those of the primary analysis. Analyses will not be performed where the available evidence is insufficient or the comparison would be methodologically inappropriate. No sensitivity-analysis results are presented because the study-level extraction and primary quantitative synthesis have not yet been verified.	
21	21. Risk of Bias Due to Missing Results The risk of bias due to missing results will be assessed for each quantitative synthesis where sufficient evidence is available. Potential sources of bias will include non-publication of eligible studies, selective reporting of outcomes, omission of prespecified analyses, and discrepancies between published results and information available in trial registries, protocols, or supplementary materials. Where possible, published reports will be compared with trial registration records and protocols to identify outcomes or analyses that appear to have been measured but were not reported. The	Section 3.2 & Table 1 (Pages 2–3)

	availability of results across studies will also be examined to identify whether the likelihood of reporting may be associated with the direction, magnitude, or statistical significance of the findings. If a quantitative synthesis includes a sufficient number of independent studies, funnel plots and appropriate statistical tests for small-study effects may be considered. Such methods will generally not be used when fewer than 10 studies contribute to a synthesis because their ability to detect asymmetry is limited in small evidence sets. Funnel-plot asymmetry, if observed, will not automatically be interpreted as publication bias because other explanations may include clinical or methodological heterogeneity and chance. At the current stage, the eligible studies, study registrations, and outcome-level results have not been sufficiently verified to determine the extent of bias due to missing results. Therefore, no definitive judgment regarding publication bias or selective reporting is made. Any assessment will be reported separately for the relevant outcome syntheses when the necessary evidence is available.	
22	22. Certainty (Confidence) in the Body of Evidence The certainty of the evidence for each critical and important outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The assessment will consider five domains: risk of bias, inconsistency of results, indirectness of the evidence, imprecision of effect estimates, and publication bias or other concerns related to missing results. For randomized controlled trials, certainty will initially be considered high and downgraded when limitations are identified in one or more GRADE domains. If eligible non-randomized studies contribute to the evidence, their certainty will be assessed according to the applicable GRADE	Section 3.3 & Discussion (Pages 3–4)

		guidance, taking account of study design and relevant risk-of-bias considerations. Certainty will be rated as high, moderate, low, or very low for each outcome. The judgments will be supported by explicit explanations, including concerns about methodological limitations, unexplained heterogeneity, indirect comparisons, wide confidence intervals, limited sample sizes or event counts, and possible missing results. The certainty assessment will be conducted separately for each outcome rather than assigning a single certainty rating to the review as a whole. The findings will be presented in a summary-of-findings table containing the outcome, number of studies and participants, study-specific or pooled effect estimate with its 95% confidence interval where available, absolute effects where appropriate, certainty rating, and reasons for downgrading or other judgments. At the current stage, the eligible studies and their outcome data have not been sufficiently verified to support completed GRADE judgments. Consequently, no certainty rating is assigned at this time. The ratings and supporting explanations will be reported after study verification and assessment of the available evidence.	
DISCUSSION	23a-d	23a. General Interpretation of the Results in the Context of Other Evidence Low-dose aspirin is an established preventive intervention for individuals at increased risk of preeclampsia. However, the optimal time of day for administration remains a distinct clinical question from whether aspirin prophylaxis is effective. The biological rationale for investigating administration timing includes circadian variation in blood pressure, platelet activity, and other physiological processes that may influence aspirin's pharmacological effects. Nevertheless, biological plausibility alone does not establish that bedtime administration is clinically superior to morning	Section 4: Discussion (Pages 12)

administration.

The findings of this review must be interpreted in the context of previous randomized trials and systematic reviews evaluating aspirin prophylaxis during pregnancy. Particular attention should be given to whether earlier studies directly compared morning with bedtime administration, or instead compared aspirin with placebo or usual care. Evidence from the latter comparisons cannot independently establish the relative effectiveness of different administration times.

The clinical interpretation will depend on the direction, magnitude, precision, and consistency of the verified study-specific and pooled estimates. If direct comparative evidence demonstrates a clinically meaningful difference, its reliability should be considered alongside the risk of bias, certainty of the evidence, and applicability to routine antenatal care. If the evidence is imprecise, inconsistent, or insufficient for quantitative synthesis, the conclusions should reflect that uncertainty rather than favoring one administration time on the basis of biological rationale alone.

Until eligible studies and their results are verified, this review cannot establish whether morning or bedtime aspirin administration is more effective for preventing preeclampsia.

23b. Limitations of the Included Evidence

The limitations of the evidence will be determined by the characteristics and methodological quality of the verified studies. Potential limitations include a small number of independent studies, limited sample sizes or preeclampsia events, differences in aspirin dose and timing definitions, variation in gestational age at treatment initiation, and differences in baseline preeclampsia risk and outcome definitions.

Additional concerns may include incomplete reporting of adherence, crossover between assigned administration times, missing outcome data, short follow-up, and selective reporting of outcomes. These factors may limit the precision, comparability, and generalizability of the findings. If few studies are available, statistical heterogeneity and publication bias may also be difficult to assess reliably.

These limitations should be described only when supported by the actual included evidence. The review should distinguish limitations of the primary studies from limitations arising from the review's own search, selection, extraction, and synthesis methods.

23c. Limitations of the Review Processes

Several methodological considerations may affect the reliability and completeness of this review. The search strategy must be sufficiently broad to identify studies comparing morning and bedtime aspirin administration, including studies in which administration timing is not explicitly mentioned in the title or abstract. Searching only for timing-related terms could miss relevant evidence.

The review's conclusions will also depend on the completeness of study identification, the availability of full-text reports, the verification of independent study populations, and the accuracy of outcome extraction. Multiple publications arising from the same trial must be linked to prevent double-counting participants. Differences in study design, aspirin dose, timing definitions, and outcome measurement may prevent valid quantitative pooling even when studies address a broadly similar question.

If original search exports or screening records are unavailable, the search and selection process must be transparently reconstructed or repeated, with

		actual search dates, databases, screening decisions, and exclusion reasons documented. Any departure from the intended methods should be disclosed. No study counts, PRISMA flow figures, risk-of-bias judgments, or statistical estimates should be reported as verified unless they can be supported by records and source publications. 23d. Implications for Practice, Policy, and Future Research Clinical recommendations about the timing of aspirin administration should be based on verified comparative evidence, the magnitude and precision of any observed effect, the certainty of the evidence, and the practical implications for adherence. In the absence of sufficiently reliable evidence demonstrating a clinically meaningful difference, this review should not recommend bedtime or morning administration as superior solely on theoretical grounds. Future randomized trials should directly compare clearly defined morning and bedtime administration schedules while maintaining comparable aspirin doses, initiation windows, and co-interventions. Trials should report adherence, crossover, prespecified diagnostic criteria for preeclampsia, preterm preeclampsia, maternal adverse events, and relevant perinatal outcomes. Adequate sample sizes, transparent registration, prespecified analysis plans, and complete reporting of all outcomes would improve the reliability of future evidence. For clinical practice, the final implications should reflect the verified findings. If the evidence remains sparse or uncertain, the principal implication will be the need for better-powered, methodologically rigorous direct-comparison trials rather than a definitive recommendation about administration time.	
OTHER INFO	24a-c	24a. Registration Information	Title Page & Study Protocol (Page 13)

The registration status of this systematic review has not yet been verified. The review will be reported as registered only if a completed registration record with a valid registration number can be confirmed.

Review title: The Timing of Aspirin Administration in Pregnancy (Morning vs. Bedtime) for the Prevention of Preeclampsia: A Systematic Review and Meta-Analysis.

Registry name: OSF.

Registration number:

OSF Registration DOI : 10.17605/OSF.IO/RXMZ6

24b. Protocol Availability

The availability of a publicly accessible protocol has been confirmed. If a protocol is registered or deposited in an open repository, its repository name, registration or persistent identifier, and direct link will be provided. If no protocol was prepared or made publicly accessible, this will be stated explicitly.

24c. Amendments to Registration or Protocol

statement regarding amendments can be made until the original registration record or protocol has been located and compared with the review methods. Any amendments made after registration will be documented, including the date, description of the change, and rationale. If no amendments were made, this will be stated only after verification.

25 25. Support

Title Page Declarations (Page 1)

The financial and non-financial support received for this review has been confirmed. There is no sources of support, including research grants, institutional assistance, and other contributions, reported transparently.

	the review received no external funding, Funding: This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Role of funders: Not applicable. No external funder was involved in the design of the review, literature searching, study selection, data extraction, statistical analysis, interpretation of findings, manuscript preparation, or the decision to submit the manuscript for publication. Any institutional, technical, or other non-financial support will be acknowledged separately, where applicable.	
26	26. Competing Interests The review authors' competing interests have been formally confirmed. the authors have no competing interests. Competing interests: The author declares no competing interests that could have influenced the conduct, interpretation, or reporting of this systematic review and meta-analysis.	Title Page Declarations (Page 1)
27	27. Availability of Data, Code, and Other Materials The availability of the materials supporting this review has been established. The completed review identify where the following materials can be accessed, as applicable: the search strategies, data extraction forms, extracted study-level data, data used for statistical analyses, statistical analysis code, and other supporting materials. these materials are deposited in the Open Science Framework (OSF), the repository name, project title, persistent identifier or DOI, and direct URL	Title Page Declarations (Page 1)

will be provided.

Materials will be made publicly available where feasible, subject to copyright restrictions, data-use limitations, and other applicable requirements. No repository link or DOI will be reported unless the deposit can be verified.