JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Jillian T. Henderson, PhD, MPH; Kimberly K. Vesco, MD, MPH; Caitlyn A. Senger, MPH; Rachel G. Thomas, MPH; Nadia Redmond, MSPH

IMPORTANCE Preeclampsia is a hypertensive disorder of pregnancy that poses serious maternal and infant health risks. Previous systematic reviews have established benefits of low-dose aspirin taken during pregnancy to prevent preeclampsia and its sequelae.

OBJECTIVE To update evidence for the US Preventive Services Task Force (USPSTF) on effectiveness of aspirin use in preventing preeclampsia in individuals at increased risk based on clinical risk factors or measurements associated with higher disease incidence than in the general population.

DATA SOURCES Studies from previous USPSTF review (2014), literature published January 2013 through May 15, 2020, in MEDLINE, PubMed (for publisher-supplied records only), EMBASE, and Cochrane Central Register of Controlled Trials. Ongoing surveillance through January 22, 2021.

STUDY SELECTION Good- and fair-quality randomized clinical trials (RCTs) of low-dose aspirin use during pregnancy to prevent preeclampsia among individuals at increased risk; studies conducted in general populations to evaluate potential harms.

DATA EXTRACTION AND SYNTHESIS Dual article screening and risk-of-bias assessment. Study data abstracted into prespecified forms, checked for accuracy. Random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Diagnosis of preeclampsia; adverse pregnancy health outcomes and complications including eclampsia, perinatal mortality, preterm birth, small for gestational age, and potential bleeding harms or infant/child harms from aspirin exposure.

RESULTS A total of 23 randomized clinical trials (RCTs) (N = 26 952) were included; 18 were conducted among participants at increased preeclampsia risk. Aspirin dosages ranged from 50 mg/d to 150 mg/d. Most trials enrolled majority White populations selected based on a range of risk factors. The incidence of preeclampsia among the trials of participants at increased risk ranged from 4% to 30%. Aspirin use was significantly associated with lower risk of preeclampsia (pooled relative risk [RR], 0.85 [95% CI, 0.75-0.95]; 16 RCTs [n = 14 093]; I^2 = 0%), perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; 11 RCTs [n = 13 860]; I^2 = 0%), preterm birth (pooled RR, 0.80 [95% CI, 0.67-0.95]; 13 RCTs [n = 13 619]; I^2 = 49%), and intrauterine growth restriction (pooled RR, 0.82 [95% CI, 0.68-0.99]; 16 RCTs [n = 14 385]; I^2 = 41%). There were no significant associations of aspirin use with risk of postpartum hemorrhage (pooled RR, 1.03 [95% CI, 0.94-1.12]; 9 RCTs [n = 23 133]; I^2 = 0%) and other bleeding-related harms, or with rare perinatal or longer-term harms. Absolute risk reductions for preeclampsia associated with aspirin use ranged from −1% to −6% across larger trials (n >300) and were greater in smaller trials. For perinatal mortality, absolute risk reductions ranged from 0.5% to 1.1% in the 3 largest trials.

CONCLUSIONS AND RELEVANCE Daily low-dose aspirin during pregnancy was associated with lower risks of serious perinatal outcomes for individuals at increased risk for preeclampsia, without evident harms.

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Supplemental content

Author Affiliations: Kaiser Permanente Evidence-based Practice Center, Center for Health Research, Kaiser Permanente, Portland, Oregon.

Corresponding Author: Jillian T. Henderson, PhD, MPH, Kaiser Permanente Evidence-based Practice Center, Center for Health Research, Kaiser Permanente Northwest, 3800 N Interstate Ave, Portland, OR 97227 (Jillian.T.Henderson@kpchr.org).

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Preeclampsia is a systemic hypertensive disorder of pregnancy thought to arise from abnormal placentation and systemic inflammatory processes and characterized by increased blood pressure, accompanied by proteinuria or other signs.[1,2] The condition can vary in severity, have an unpredictable course, and increases risks for serious maternal health complications such as eclamptic seizures, stroke, organ damage, and death.[3-10] It also poses serious neonatal and infant risks, including intrauterine growth restriction, low birth weight, preterm birth, placental abruption, stillbirth, and neonatal death.[2,11,12]

The estimated incidence of preeclampsia in the US increased from 38.4 per 1000 deliveries in 2005 to 46.6 per 1000 deliveries in 2014,[13] and the majority of this increase has been cases of preeclampsia with severe features (11.6 to 17.4 cases per 1000 deliveries) and preeclampsia occurring in the presence of chronic hypertension (3.7 to 6.7 per 1000 deliveries).[13] Inequities in health are observed, especially for Black women giving birth in the US; preeclampsia was estimated to occur in 69.8 per 1000 deliveries among Black women compared with 43.4 per 1000 deliveries among White women, contributing to higher overall maternal morality for Black women.[13,14]

In 2014 the US Preventive Services Task Force (USPSTF) recommended the prescription of low-dose (81 mg/d) aspirin after 12 weeks of gestation to asymptomatic pregnant women who are at high risk for preeclampsia (B recommendation).[15] The current review of the evidence regarding the effectiveness of aspirin in reducing the risk for preeclampsia and adverse maternal, perinatal, and child outcomes, along with potential harms of aspirin use, was conducted to inform a USPSTF update to its current recommendation.

Methods

Scope of Review

An analytic framework was developed with 3 key questions (KQs) (**Figure 1**) that examined the effectiveness of aspirin in reducing adverse maternal, perinatal, child, or combined health outcomes in studies conducted among pregnant persons selected based on the presence of clinical risk factors or physical measures known to be associated with an increased risk of preeclampsia (KQ1); in preventing preeclampsia (KQ2); and the potential harms of aspirin use to prevent preeclampsia during pregnancy (KQ3). Additional methodological details are publicly available in the full evidence report.[17]

Data Sources and Searches

To identify studies published since the previous review,[18] literature searches were conducted from January 2013 through May 15, 2020, in MEDLINE, PubMed (for publisher-supplied records only), EMBASE, and the Cochrane Central Register of Controlled Trials (eMethods in the Supplement). Additional studies were sought by reviewing reference lists of other systematic reviews. Ongoing surveillance was conducted after May 2020 through January 22, 2021, to identify newly published studies that might affect the findings of the review. This was accomplished through article alerts and targeted searches of journals with a high impact factor and journals relevant to the topic. The last surveillance on January 22, 2021, identified no new studies.

Study Selection

Two reviewers independently evaluated articles from the previous review in addition to citations and full-text articles from the literature searches against prespecified inclusion criteria (**Figure 2**; eTable 1 in the Supplement). For the KQ1 and KQ2 questions of effectiveness, randomized clinical trials (RCTs) and individual participant data meta-analyses of pregnant persons at increased risk for preeclampsia were considered for inclusion. Risk of preeclampsia was determined based on personal sociodemographic characteristics, medical history, diagnostic measurements or assays, or risk prediction models. For KQ3 evaluating harms, these criteria were expanded to include RCTs conducted in lower-risk or average-risk populations and comparative observational studies of pregnant persons exposed to aspirin for preeclampsia prevention over the course of pregnancy, as well as their similarly exposed fetuses, infants, and children. Studies limited to persons seeking fertility treatments were not included. Only studies of daily aspirin (≥50 mg/d) for the primary prevention of preeclampsia were considered for inclusion; studies evaluating nonaspirin antiplatelet medications or aspirin combined with other potentially active interventions (eg, dietary supplements, weight loss), or studies of aspirin aimed at preventing other complications of pregnancy such as miscarriage, were excluded. The review was limited to studies conducted in countries with "very high" Human Development Index (2016) scores, as published by the United Nations Development Programme.[19] Studies were also limited to those published in English and deemed good or fair quality based on USPSTF quality rating standards.[16]

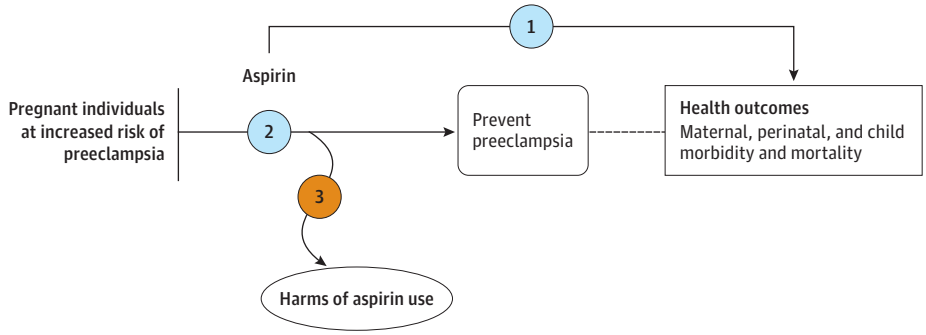
Data Extraction and Quality Assessment

Two reviewers applied USPSTF design-specific criteria[16] to assess the methodological quality of all eligible studies, and each study was assigned a quality rating of "good," "fair," or "poor" (eTable 2 in the Supplement). Discordant quality ratings were resolved by discussion and adjudicated by a third reviewer as needed. Studies rated as poor quality were excluded from the review. Good-quality RCTs were those that met all or nearly all prespecified quality criteria. Fair-quality studies did not meet all criteria but did not have serious threats to their internal validity related to design, execution, or reporting. Intervention studies rated as poor quality had several important limitations, including at least 1 of the following risks of bias: very high attrition (defined as >40%); differential attrition between intervention groups (defined as >20%); lack of baseline comparability between groups without adjustment; or problematic issues in trial conduct, analysis, or reporting of results. One reviewer extracted data from all included studies rated as fair or good quality directly into evidence tables, and a second reviewer checked the data accuracy.

Data Synthesis and Analysis

Data were synthesized separately for each KQ, and tables were created to describe study results for all included outcomes, with stratification by intervention and study population characteristics. Summary tables were used to describe important features of the evidence, including study design and setting, internal validity, and important characteristics about patients and interventions. Pooled estimates of the relative risks of health outcomes associated with aspirin use were generated using random-effects

Figure 1. Analytical Framework: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality



Key questions

1 Does aspirin reduce adverse maternal, perinatal, child, or combined health outcomes in pregnant persons at increased risk of preeclampsia?
a. Does effectiveness of aspirin for reducing adverse health outcomes vary by subpopulations defined by personal characteristics or preeclampsia factors?

2 Does aspirin prevent preeclampsia in pregnant persons at increased risk for preeclampsia?
a. Does effectiveness of aspirin for reducing preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia factors?

3 What are the harms of aspirin use to prevent preeclampsia during pregnancy?
a. Do the harms of aspirin use to prevent preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a health outcome that immediately follows an intermediate outcome. For additional details see the USPSTF Procedure Manual.[16]

restricted maximum likelihood models (REMLs) with Knapp-Hartung correction.[20,21] This analytic approach overcomes limitations of other random-effects models that have been found to generate overly precise confidence limits, especially when pooling fewer than 20 studies.[22] For results approaching the margins of statistical significance and for analyses with low τ values, sensitivity analyses with the Knapp-Hartung correction were used to adjust the standard errors, and the more conservative results were reported. For rare outcomes (ie, perinatal mortality), sensitivity analyses were conducted using the Peto odds ratio method,[23] as well as pooled analyses including and excluding studies that had no events in either study group, to assess the robustness of the final REML risk ratio pooled estimates.[24]

To examine subgroup differences, stratified forest plots were generated using the Cochran *Q* statistical test of group differences and REML meta-regression analyses using the Knapp-Hartung correction; the more conservative result was reported. Variables anticipated a priori to be potential sources of heterogeneity included aspirin dosage, timing, and duration; population risk characteristics (eg, incidence of preeclampsia in the control condition, strategy for selecting participants); study size; and control condition (ie, placebo vs no treatment). For comparisons of effects by population risk of preeclampsia, studies in which more than 12% of participants developed preeclampsia in the control group were compared with studies having lower incidence rates. This threshold was selected to distinguish studies conducted in the highest-risk populations (≈3× general population risk). Studies that used laboratory or imaging tests were compared with those relying only on clinical history and examinations. Sensitivity analyses were conducted to estimate pooled effects under more and less conservative statistical approaches. For each KQ, the statistical heterogeneity of included studies was estimated with I^2 statistics and τ.[2] The distribution of trial results was examined with funnel plots and Peters tests to assess whether there was evidence of small-study effects.[25-27]

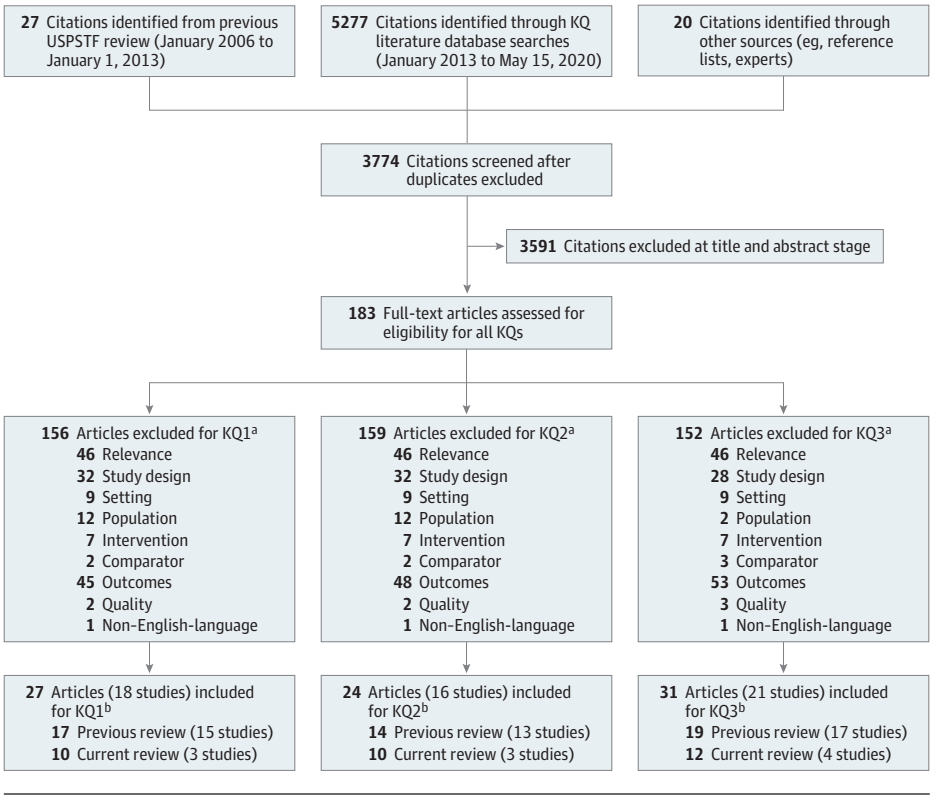
Stata version 16.1 (StataCorp) was used for all analyses. All significance testing was 2-sided, and results were considered statistically significant if $P < .05$.

The strength of evidence was rated for each KQ based on consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (ie, study limitations).

Results

Two reviewers evaluated 3749 citations and 183 full-text articles against inclusion criteria, and 23 studies (33 articles) met inclusion criteria for this systematic review (Figure 2). Nineteen RCTs[28-46] were carried forward from the previous USPSTF report, and 4 new RCTs[47-50] were identified for inclusion (**Table 1**). For KQ1 and KQ2, 18 trials were included that enrolled pregnant individuals at increased risk of preeclampsia.[28-31,35-40,42,44-46,48-50] For KQ3, 5 additional trials enrolling pregnant individuals at average risk of preeclampsia were included.[32,33,41,43,47] Six large, multisite trials were included in the review (for KQ1 and KQ2: the US-based Maternal Fetal Medicine Unit Network Trial in High Risk Women [MFMU-HR] [n = 2539],[40] the Collaborative Low-dose Aspirin Study in Pregnancy [CLASP] trial [n = 9364],[36] and the Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention [ASPRE] trial

Figure 2. Literature Search Flow Diagram: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality



KQ indicates key question; USPSTF, US Preventive Services Task Force.

[a] Reason for exclusion: *Relevance:* Study aim not relevant. *Study design:* Not a randomized clinical or case-control study. *Setting:* Excluded on the basis of setting alone (eg, emergency departments, research laboratories, worksites, inpatient/residential departments); setting not linked to health care. *Population:* Population not at increased risk (eg, nulliparous women). *Intervention:* Nonapplicable intervention (eg, nonaspirin antiplatelet medications or aspirin combined with other potentially active interventions). *Comparator:* Control condition other than placebo or no treatment. *Outcomes:* No relevant outcomes. *Quality:* Study was poor quality. *Non–English-language:* Publication was not in English.

[b] Studies could be included for more than 1 KQ.

[n = 1776][48]; for KQ3: the Maternal Fetal Medicine Unit Network Trial enrolling low- and average-risk participants [MFMU-LR] [n = 3135],[33] the Essai Régional Aspirine Mère-Enfant study [ERASME] [n = 3294],[43] and the Barbados Low Dose Aspirin Study in Pregnancy [BLASP] [n = 3647]).[41] The inclusion and exclusion criteria in the trials were usually well described, but details on baseline demographic characteristics and risk factors of enrolled participants were often sparsely or inconsistently reported (Table 1).

A variety of study procedures and criteria were used to identify populations of pregnant persons at increased risk for preeclampsia (Table 1; eTable 3 in the Supplement). The most common method was examination of participant characteristics and personal or family medical history (eg, age, parity, multifetal gestation, history of hypertensive disorders, history of pregnancy complications). History of hypertensive disorders, alone or in combination with other risk factors, was used as the primary method to identify trial participants in 10 studies,[29,30,34,36,38-40,42,45,46] and multifetal gestation was used in 6 trials.[30,35,36,39,40,45] Other clinical risk factors used included metabolic disease[39,45]; diabetes (prepregnancy or gestational),[40,46] history of small for gestational age/intrauterine growth restriction (SGA/IUGR),[29,42,46] spontaneous abortion,[39,45,46] or stillbirth[29,42]; renal disease[36,38]; and maternal age.[36,39,45] Risk assessment also frequently involved diagnostic measurements or assays, either as the primary means to identify individuals at risk or in combination with medical history and personal characteristics. Abnormal Doppler readings were used in 6 studies.[31,44,46,48-50] Other methods included angiotensin II sensitivity,[28] a positive rollover test result,[30] second trimester hemoglobin concentration,[37] and use of a prediction model that combined maternal demographic factors and clinical measurements.[48]

Included trials varied widely in timing and dosages of aspirin treatment (Table 1). The gestational age at which aspirin therapy was initiated across the trials varied substantially, with 9 trials starting therapy in participants at as early as 11 to 12 weeks of gestation and 5 trials allowing initiation to continue as late as 36 to 38 weeks of gestation. The most common date of aspirin discontinuation was delivery, but 8 trials stopped aspirin prophylaxis before delivery,[30,38,42-44,46-48] as early as 34 weeks,[43] or at the point when preeclampsia developed.[40] Aspirin dosages ranged from 50 mg/d to 150 mg/d. The majority of trials used dosages of either 60 mg/d (6 trials)[28,29,32,33,36,40] or 100 mg/d (9 trials)[30,35,38,39,42,43,45,46,50]; 2 of the newly identified trials used a higher dose of 150 mg/d.[48,49] A matching placebo was the comparator in all trials except in 1 study included for harms, in which participants in the control group received usual care with no placebo.[47]

Benefits on Health Outcomes

Key Question 1. Does aspirin reduce adverse maternal, perinatal, child, or combined health outcomes in pregnant persons at increased risk of preeclampsia?

Key Question 1a. Does the effectiveness of aspirin for reducing adverse health outcomes vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

Table 1. Characteristics of Included Studies

Source, country/countries	Study quality	No. randomized	Increased risk criteria	Aspirin dosage, mg[a]	Timing of aspirin initiation; discontinuation	Age, mean (range), y	White, %	Nulliparous, %	Previous preeclampsia, %	Chronic hypertension, %
Increased-risk population										
ASPRE Rolnik et al,[48] 2017 Spain, Italy, UK, Israel, Belgium, Greece	Good	1776	Risk prediction model findings at 11-13 wk gestation	150	11-14 wk; 36 wk	31.5[b]	67.1	67.3	10.5	6.8
Ayala et al,[45] 2013 Spain	Good	350	Receiving pregnancy care at high-risk obstetric unit owing to range of factors	100	12-16 wk; delivery[c]	30.7	NR	52.2	NR	NR
Benigni et al,[29] 1989 Italy	Fair	33	Presence of hypertension or previous history of fetal death due to placental insufficiency, severe IUGR, early-onset preeclampsia [<32 wk]	60	12 wk; delivery	31.5	NR	NR	42.7	33.3
Caspi et al,[35] 1994 Ireland	Good	48	Uncomplicated twin pregnancies	100	Start of the second trimester; delivery[d]	28.3	NR	36	NR	2
CLASP,[36] 1994 US, Australia, Canada, Germany, Spain, Hong Kong, Ireland, The Netherlands, New Zealand, Sweden, UK, Argentina, Belgium, Malaysia, Russia, United Arab Emirates	Good	9364	Increased risk determined by clinician based on range of factors including obstetric history, family history, patient and pregnancy characteristics	60	12 to 32 wk; delivery	28.5	NR	27.9	NR	20
Davies et al,[37] 1995 UK	Fair	122	Hemoglobin concentration greater than 13.2 g/dL	75	18 wk; delivery	25.0	95.8	100	0	0
Gallery et al,[38] 1997 Australia	Fair	108	Chronic hypertension or previous early, severe preeclampsia	100	17 to 19 wk; 2 wk before planned delivery	28.5 (22-38)	95.5	42.5	19.3	54.7
Grab et al,[42] 2000 Germany	Fair	43	Early IUGR, impaired uteroplacental blood, chronic hypertension or previous stillbirth, growth restriction, or preeclampsia	100	18 wk; 38 wk	NR	NR	NR	41.9	44.2
Hermida et al,[39] 1997 Spain	Good	100	Receiving pregnancy care at high-risk hospital unit owing to broad range of preeclampsia factors	100	12 to 16 wk; delivery[c]	30.2	100	NR	NR	NR
McParland et al,[31] 1990 UK	Fair	106	Nulliparous with persistent abnormal Doppler flow-velocity waveforms at 24 wk gestation	75	24 wk; delivery	26.1	69.0	100	NR	NR
MFMU-HR Caritis et al,[40] 1998 US	Good	2539	Presence of diabetes, chronic hypertension, multifetal gestation, previous preeclampsia	60	13 to 26 wk; delivery or if preeclampsia developed	26.5	32.7	NR	NR	NR

(continued)

Table 1. Characteristics of Included Studies (continued)

Source, country/countries	Study quality	No. randomized	Increased risk criteria	Aspirin dosage, mg[a]	Timing of aspirin initiation; discontinuation	Age, mean (range), y	White, %	Nulliparous, %	Previous preeclampsia, %	Chronic hypertension, %
Morris et al,[50] 1996 Australia	Fair	102	Nulliparous with abnormal Doppler ultrasound findings at 17-19 wk gestation	100	18 wk; NR	23.8	NR	100	NR	NR
Scazzocchio et al,[49] 2017 Spain	Good	186	Abnormal Doppler ultrasound findings at 11-14 wk gestation	150	11 to 14 wk; delivery[e]	32.9	NR	63.2	0	0
Schiff et al,[30] 1989 Israel	Good	65	Nulliparity, twin gestation, history of preeclampsia, or positive rollover test	100	28 or 29 wk to 38 wk	27.4	100	NR	16.9	0
Viinikka et al,[34] 1993 Finland	Fair	208	Presence of hypertension or previous severe preeclampsia	50	16 wk; delivery	33.0	NR	24.5	11.1	88.9
Villa et al,[46] 2013 Finland	Fair	152	Range of preeclampsia risk factors accompanied by abnormal Doppler ultrasound findings at 12-14 wk gestation	100	12 to 14 wk; 35 wk or delivery (whichever came first)	30.9 (20-40)	NR	20.7	30.6	16.5
Wallenburg et al,[28] 1986 The Netherlands	Good	46	Angiotensin-II sensitivity infusion and blood pressure test	60	28 wk; delivery[d]	24 (17-38)	NR	100	0	0
Yu et al,[44] 2003 UK, Chile, South Africa, Brazil	Good	560	Abnormal Doppler ultrasound findings at 22-24 wk gestation	150	22 to 24 wk; 36 wk	29 (23-33)[b]	62.3	25.1	9.9	0
General population (included for harms only)										
Hauth et al,[32] 1993 US	Good	606	NA	60	No later than 22 wk; delivery	20.4	28.5	100	NR	0
MFMU-LR Sibai et al,[33] 1993 US	Good	3135	NA	60	13 to 25 wk; delivery	20.5	17.9	100	NR	0
Mone et al,[47] 2018 Ireland	Fair	362	NA	75	11 to 13 wk; 36 wk[e]	33.5 (19-44)	96.8	100	NR	0
Rotchell et al,[41] 1998 Barbados	Good	3647	NA	75	12 to 32 wk; delivery	NR	NR	44	NR	0.4
Subtil et al,[43] 2003 France, Belgium	Good	3294	NA	100	14 to 20 wk; 34 wk	24.7	NR	100	NR	0

Abbreviations: ASPRE, Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; IUGR, intrauterine growth restriction; MFMU-LR, Maternal Fetal Medicine Unit Network Trial enrolling low- and average-risk participants; NA, not applicable; NR, not reported.

[a] All studies placebo-controlled except for Mone et al,[47] which had a usual-care control.

[b] Median (range).

[c] Treatment time of day randomly assigned (morning, afternoon, or evening).

[d] Treatment time of day, morning. [e]Treatment time of day, evening.

Table 2. Summary of Meta-analysis Results

	No. of studies reporting outcome (No. of observations randomized)	Pooled analysis, No. of studies (No. analyzed)[a]	Pooled RR, random-effects model (95% CI)[b]	I^2, %	τ^2	Relative risk, range	ARD	Relative risk, median (IQR)	ARD (range)
Perinatal mortality	15 (15 527)	11 (13 860)	0.79 (0.66-0.96)	0.0	0.0	0.31-5.15	−6.3 to 2.9	0.96 (0.59-1.10)	0.0 (−1.1 to 0.5)
Preterm birth	13 (15 213)	13 (13 619)	0.80 (0.67-0.95)	48.7	0.02	0.12-1.03	−19.5 to 0	0.65 (0.35-0.90)	−5.7 (−12.9 to −3.0)
SGA/IUGR	16 (15 767)	16 (14 385)	0.82 (0.68-0.99)	41.2	0.04	0.30-1.22	−25.7 to 4.9	0.63 (0.48-0.97)	−4.6 (−8.9 to −0.2)
Preeclampsia	16 (15 767)	16 (14 093)	0.85 (0.75-0.95)	0.0	0.0	0.07-1.43	−30.4 to 4.1	0.72 (0.31-0.89)	−4.1 (−8.4 to −1.3)
Postpartum hemorrhage	11 (23 583)	9 (23 133)	1.03 (0.94-1.12)	0.0	0.0	0.38-2.84	−4.2 to 9.1	1.02 (0.94-1.23)	0.2 (−0.4 to 0.9)
Placental abruption	13 (25 761)	10 (24 970)	1.15 (0.76-1.72)	25.3	0.07	0.64-5.56	−0.6 to 1.8	1.21 (0.96-2.07)	0.3 (0 to 0.6)
Fetal intracranial bleeding	9 (23 959)	6 (23 719)	0.90 (0.51-1.57)	19.2	0.06	0.17-2.06	−0.3 to 0.6	0.94 (0.74-1.08)	0.0 (−0.1 to 0.0)

Abbreviations: ARD, absolute risk difference; RR, risk ratio; SGA/IUGR, small for gestational age/intrauterine growth restriction.

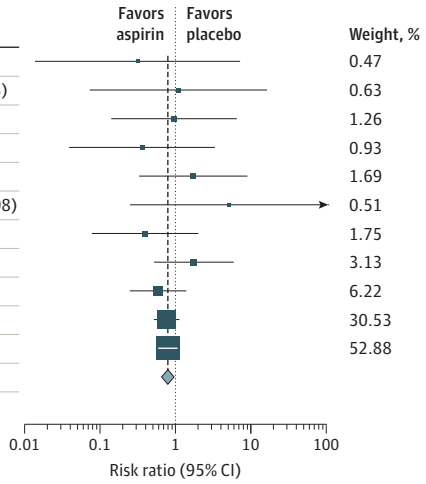
[a] Studies that reported no events in both study groups were excluded from the pooled analysis.

[b] Restricted maximum likelihood model with Knapp-Hartung confidence intervals.

Figure 3. Perinatal Mortality, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total: Aspirin	Events, No./total: Placebo	Risk ratio (95% CI)	Weight, %
Benigni et al,[29] 1989	NR	60	0/17	1/16	0.31 (0.01-7.21)	0.47
Wallenburg et al,[28] 1986	30	60	1/21	1/23	1.10 (0.07-16.43)	0.63
Caspi et al,[35] 1994	9	100	2/48	2/46	0.96 (0.14-6.52)	1.26
McParland et al,[31] 1990	19	75	1/48	3/52	0.36 (0.04-3.35)	0.93
Gallery et al,[38] 1997	NR	100	4/58	2/50	1.72 (0.33-9.02)	1.69
Viinikka et al,[34] 1993	11	50	2/97	0/100	5.15 (0.25-105.98)	0.51
Ayala et al,[45] 2013	13	100	2/176	5/174	0.40 (0.08-2.01)	1.75
Yu et al,[44] 2003	19	150	7/276	4/278	1.76 (0.52-5.95)	3.13
ASPRE,[48] 2017	11	150	8/798	14/822	0.59 (0.25-1.40)	6.22
MFMU-HR,[40] 1998	20	60	43/1254	56/1249	0.76 (0.52-1.13)	30.53
CLASP,[36] 1994	8	60	77/4123	97/4134	0.80 (0.59-1.07)	52.88
Overall					0.79 (0.66-0.96)	

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0.00\%$
Test of $\theta = 1$; $t(10) = -2.70$; $P = .02$



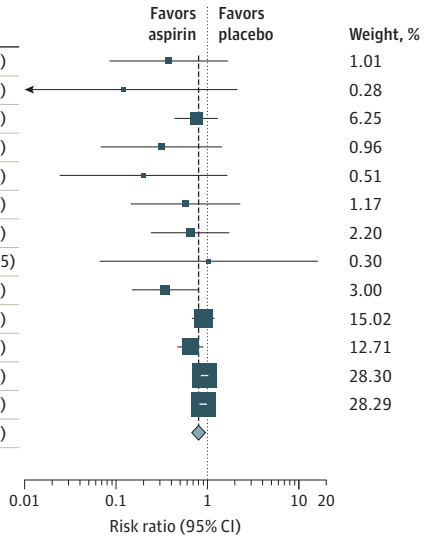
Random-effects restricted maximum likelihood model with Knapp-Hartung confidence intervals. Excluded 3 studies with 0 events in both groups. Size of each box (point estimate of each study) reflects the Weight column indicating the influence an individual study has on the pooled results. ASPRE indicates Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; MFMU-HR, Maternal Fetal Medicine Unit Network Trial in High Risk Women; RR, risk ratio.

Eighteen trials (n = 15 908) reported maternal, perinatal, or child health outcomes for daily aspirin use (50 mg/d to 150 mg/d) compared with a matching placebo starting as early as 11 weeks or as late as 32 weeks of gestation and continuing until late pregnancy or delivery. In pooled analyses, aspirin was consistently associated with a reduced risk of perinatal mortality, preterm birth, and SGA/IUGR (**Table 2**). Fifteen trials reported perinatal mortality (n = 15 527). No individual study reported a statistically significant difference in perinatal mortality, but all were underpowered for the outcome; however, the pooled estimate showed a statistically significant 21% reduction in the risk of perinatal mortality associated with aspirin use (pooled risk ratio [RR], 0.79 [95% CI, 0.66-0.96]; 11 RCTs [n = 13 860]; I^2 = 0%) (**Figure 3**). Thirteen trials reported on preterm birth (<37 weeks of gestation) (n = 15 213). Results across these trials were consistently in the direction of a preventive benefit of daily aspirin use, with no trial finding more cases of preterm birth in the aspirin group than in the placebo group. The pooled result showed an estimated 20% reduced risk of preterm birth associated with intervention (pooled RR, 0.80 [95% CI, 0.67-0.95]; 13 RCTs [n = 13 619]; I^2 = 49%) (**Figure 4**). Trials rarely reported cases of spontaneous preterm birth separately from induced preterm birth, and few studies reported the number of cases of early preterm (<34 weeks of gestation) and extremely preterm (<28 weeks of gestation) birth. Sixteen trials reported on

Figure 4. Preterm Birth Before 37 Weeks' Gestation, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	2/17	5/16	0.38 (0.08-1.67)	1.01
Wallenburg et al,[28] 1986	30	60	0/21	4/23	0.12 (0.01-2.12)	0.28
Caspi et al,[35] 1994	9	100	11/24	14/23	0.75 (0.44-1.30)	6.25
Schiff et al,[30] 1989	23	100	2/34	6/32	0.31 (0.07-1.44)	0.96
Hermida et al,[39] 1997	14	100	1/50	5/50	0.20 (0.02-1.65)	0.51
Morris et al,[50] 1996	14	100	3/52	5/50	0.58 (0.15-2.29)	1.17
Gallery et al,[38] 1997	NR	100	6/58	8/50	0.65 (0.24-1.74)	2.20
Davies et al,[37] 1995	12	75	1/58	1/60	1.03 (0.07-16.15)	0.30
Ayala et al,[45] 2013	13	100	7/176	20/174	0.35 (0.15-0.80)	3.00
Yu et al,[44] 2003	19	150	67/276	75/278	0.90 (0.68-1.20)	15.02
ASPRE,[48] 2017	11	150	53/798	84/822	0.65 (0.47-0.90)	12.71
HFMU-HR,[40] 1998	20	60	502/1254	537/1249	0.93 (0.85-1.02)	28.30
CLASP,[36] 1994	8	60	686/3992	761/3982	0.90 (0.82-0.99)	28.29
Overall					0.80 (0.67-0.95)	

Heterogeneity: $\tau^2 = 0.02$; $I^2 = 48.71\%$
Test of $\theta = 1$; $t(12) = -2.79$; $P = .02$

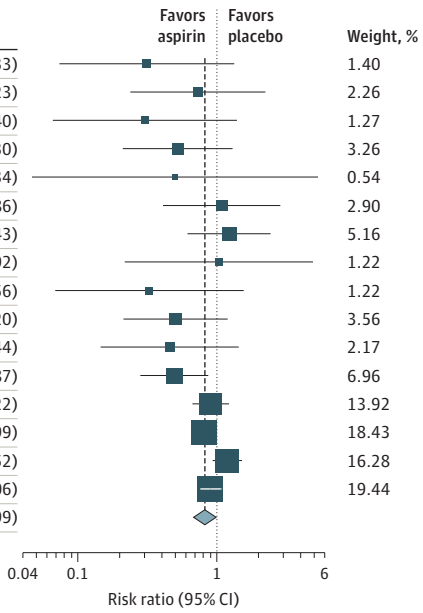


Random-effects restricted maximum likelihood model with Knapp-Hartung confidence intervals. Size of each box (point estimate of each study) reflects the Weight column indicating the influence an individual study has on the pooled results. ASPRE indicates Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; MFMU-HR, Maternal Fetal Medicine Unit Network Trial in High Risk Women; RR, risk ratio.

Figure 5. Small for Gestational Age or Intrauterine Growth Restriction, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Benigni et al,[29] 1989	NR	60	2/17	6/16	0.31 (0.07-1.33)	1.40
Wallenburg et al,[28] 1986	30	60	4/21	6/23	0.73 (0.24-2.23)	2.26
Schiff et al,[30] 1989	23	100	2/34	6/31	0.30 (0.07-1.40)	1.27
Caspi et al,[35] 1994	9	100	6/48	11/46	0.52 (0.21-1.30)	3.26
Hermida et al,[39] 1997	14	100	1/50	2/50	0.50 (0.05-5.34)	0.54
McParland et al,[31] 1990	19	75	7/48	7/52	1.08 (0.41-2.86)	2.90
Morris et al,[50] 1996	14	100	14/52	11/50	1.22 (0.62-2.43)	5.16
Davies et al,[37] 1995	12	75	3/58	3/60	1.03 (0.22-4.92)	1.22
Villa et al,[46] 2013	18	100	2/61	6/60	0.33 (0.07-1.56)	1.22
Scazzochio et al,[49] 2017	4	150	7/80	13/75	0.50 (0.21-1.20)	3.56
Viinikka et al,[34] 1993	11	50	4/97	9/100	0.46 (0.15-1.44)	2.17
Ayala et al,[45] 2013	13	100	16/176	32/174	0.49 (0.28-0.87)	6.96
Yu et al,[44] 2003	19	150	61/276	68/278	0.90 (0.67-1.22)	13.92
ASPRE,[48] 2017	11	150	148/785	187/807	0.81 (0.67-0.99)	18.43
HFMU-HR,[40] 1998	20	60	129/1254	108/1249	1.19 (0.93-1.52)	16.28
CLASP,[36] 1994	8	60	244/4123	272/4134	0.90 (0.76-1.06)	19.44
Overall					0.82 (0.68-0.99)	

Heterogeneity: $\tau^2 = 0.03$; $I^2 = 41.24\%$
Test of $\theta = 1$; $t(15) = -2.28$; $P = .04$



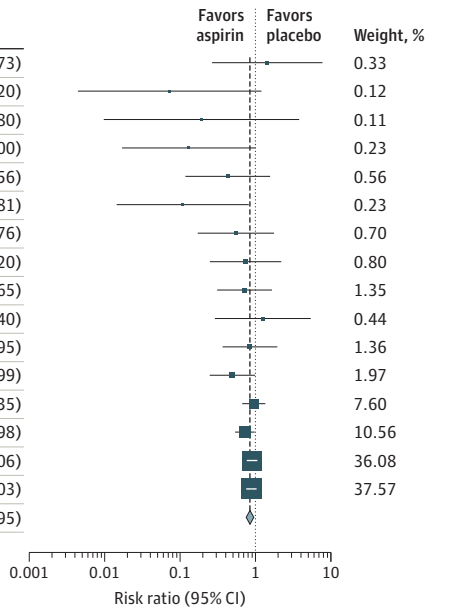
Random-effects restricted maximum likelihood model with Knapp-Hartung confidence intervals. Size of each box (point estimate of each study) reflects the Weight column indicating the influence an individual study has on the pooled results. ASPRE indicates Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; MFMU-HR, Maternal Fetal Medicine Unit Network Trial in High Risk Women; RR, risk ratio.

SGA/IUGR (n = 15 757), and all but 2[31,40] reported fewer cases in the aspirin group than in the placebo group. The pooled result indicated an estimated 18% reduced risk of having an infant that was SGA/IUGR for women who took aspirin (pooled RR, 0.82 [95% CI, 0.68-0.99]; 16 RCTs [n = 14 385]; I^2 = 41%) (**Figure 5**). Direct maternal health consequences of preeclampsia were extremely rare and include eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, stroke, organ failure, and

Figure 6. Preeclampsia, Sorted by Study Size

Source	Preeclampsia incidence with placebo, %	Aspirin dose, mg	Events, No./total		Risk ratio (95% CI)	Weight, %
			Aspirin	Placebo		
Grab et al,[42] 2000	10	100	3/22	2/21	1.43 (0.27-7.73)	0.33
Wallenburg et al,[28] 1986	30	60	0/21	7/23	0.07 (0.00-1.20)	0.12
Caspi et al,[35] 1994	9	100	0/24	2/23	0.19 (0.01-3.80)	0.11
Schiff et al,[30] 1989	23	100	1/34	7/31	0.13 (0.02-1.00)	0.23
Hermida et al,[39] 1997	14	100	3/50	7/50	0.43 (0.12-1.56)	0.56
McParland et al,[31] 1990	19	75	1/48	10/52	0.11 (0.01-0.81)	0.23
Morris et al,[50] 1996	14	100	4/52	7/50	0.55 (0.17-1.76)	0.70
Davies et al,[37] 1995	12	75	5/58	7/60	0.74 (0.25-2.20)	0.80
Villa et al,[46] 2013	18	100	8/61	11/60	0.72 (0.31-1.65)	1.35
Scazzochio et al,[49] 2017	4	150	4/80	3/75	1.25 (0.29-5.40)	0.44
Viinikka et al,[34] 1993	11	50	9/97	11/100	0.84 (0.37-1.95)	1.36
Ayala et al,[45] 2013	13	100	11/176	22/174	0.49 (0.25-0.99)	1.97
Yu et al,[44] 2003	19	150	49/276	52/278	0.95 (0.67-1.35)	7.60
ASPRE,[48] 2017	11	150	66/798	94/822	0.72 (0.54-0.98)	10.56
HFMU-HR,[40] 1998	20	60	226/1254	250/1249	0.90 (0.77-1.06)	36.08
CLASP,[36] 1994	8	60	267/3992	302/3982	0.88 (0.75-1.03)	37.57
Overall					0.85 (0.75-0.95)	

Heterogeneity: $\tau^2 = 0.00$; $I^2 = 0.00\%$
Test of $\theta = 1$; $t(15) = -3.07$; $P = .01$



Random-effects restricted maximum likelihood model with Knapp-Hartung confidence intervals. Size of each box (point estimate of each study) reflects the Weight column indicating the influence an individual study has on the pooled results. ASPRE indicates Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; MFMU-HR, Maternal Fetal Medicine Unit Network Trial in High Risk Women; RR, risk ratio.

death. Few trials reported these events, however, and pooled estimates were not possible to compute. In the few large studies with these and other maternal health outcomes, risk estimates were too imprecise to assess differences by study group.

Subgroup analyses were conducted for the outcomes of preterm birth and SGA/IUGR to explore factors associated with effect size. Although the number of trials was small, earlier aspirin initiation (before 20 weeks of gestation) was significantly associated with increased effectiveness for preventing preterm birth and SGA/IUGR, and aspirin dosages greater than 75 mg/d were significantly associated with increased effectiveness for prevention of preterm birth (eFigures 5 and 6 in the Supplement). However, there was evidence of small-study effects for the preterm birth outcome (Peters $P = .03$), and confounding of study size and other study and participant characteristics limited inferences from these subgroup comparisons. The 2 largest studies included for KQ1 reported the smallest risk reductions for all outcomes, and both of these studies started aspirin treatment later than 16 weeks of gestation and used very low daily aspirin dosages.[36,40] The number of trials was too small to conduct multivariable meta-regression.

Benefits on Preeclampsia Prevention

Key Question 2. Does aspirin prevent preeclampsia in pregnant persons at increased risk for preeclampsia?

Key Question 2a. Does the effectiveness of aspirin for reducing preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

Sixteen included RCTs (n = 15 767) reported on the effectiveness of aspirin to prevent preeclampsia (Table 2). Aspirin was associated with statistically significant reduction in the risk of preeclampsia compared with placebo (pooled RR, 0.85 [95% CI, 0.75-0.95]; 16 RCTs [n = 14 093]; $I^2 = 0\%$) (**Figure 6**). Across these studies, the incidence of preeclampsia in the placebo condition ranged from 4% to 30%, reflecting the broad range of criteria used for identifying increased-risk populations. Effects were consistent across the included studies; all but 2 small studies reported effects in the direction of a treatment benefit.[42,49] Of the 3 largest trials, 2 using 60-mg/d aspirin dosages reported approximately 10% risk reductions with confidence intervals that crossed null,[36,40] and the recent ASPRE trial using a 150-mg/d aspirin dosage reported data indicating a 28% reduced risk of preeclampsia (95% CI, 0.54-0.98).[48] Subgroup comparisons did not indicate significant differences in effects by the timing of aspirin initiation or dosage (eFigure 7 in the Supplement), and there was evidence of small-study effects for studies reporting preeclampsia incidence (Peters $P = .04$).

Nine RCTS (n = 2789) reported the effectiveness of aspirin for prevention of gestational hypertension. Meta-analysis of this outcome showed inconsistency of effects, imprecision, and higher statistical heterogeneity than for more commonly reported outcomes and did not include the 2 largest trials (pooled RR, 0.74 [95% CI, 0.46-1.18]; 9 RCTs [n = 2591]; $I^2 = 51\%$); however, the direction of association was similar to the results for preeclampsia (eFigure 1 in the Supplement).

Harms

Key Question 3. What are the harms of aspirin use to prevent preeclampsia during pregnancy?

Key Question 3a. Do the harms of aspirin use to prevent preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

Data from 21 trials[28-41,43-45,47-50] (n = 26 757) provided evidence on potential harms of daily low dosages of aspirin. Sixteen of the included trials reporting harms outcomes were conducted among pregnant individuals at increased preeclampsia risk and 5 trials[32,33,41,43,47] among average-risk populations. The most consistently reported harms outcomes were placental abruption, postpartum hemorrhage, and fetal intracranial bleeding. Other reported perinatal outcomes included cephalohematoma, congenital malformations and anomalies, and respiratory distress syndrome. No greater risk of placental abruption, postpartum hemorrhage, or fetal intracranial bleeding was identified among participants treated with aspirin compared with those who were not (Table 2), nor were there differences within studies for less commonly reported and more rare perinatal harms. There were no significant differences in these risks by aspirin dosage or gestational age at initiation. Longer-term follow-up from 1 large multicenter trial[36] was also reassuring, finding no difference in child developmental harms with aspirin use.

When comparing the trials conducted among average-risk vs increased-risk populations, there were no statistically significant differences in the risk of placental abruption (P = .41), postpartum hemorrhage (P = .12), or fetal intracranial bleeding (P = .34), and the relative risks in the increased-risk population studies were closer to 1 (Table 2; eFigures 2-4 in the Supplement). There were no statistically significant differences in the risk of abruption or postpartum hemorrhage by aspirin dosage or timing (eFigures 8 and 9 in Supplement).

Participants withdrew from treatment for a variety of reasons. It was common for participants to withdraw due to nonmedical reasons, including relocating, changing their minds about trial participation, or nonadherence with treatment. Adherence, when reported, was generally high, although reported in a variety of ways. A common reporting measure of adherence in the trials was the number of women who were found to be taking at least 80% of their treatment medication; this number ranged from 72% to 88%. Adherence based on the proportion of pills taken was selectively reported and ranged from 94% to 97%. Medical reasons for withdrawal included concerns regarding asthma attacks, increased bleeding time, increased activity of aspartate amino transferase in serum, urticaria, and epigastric pain. Women also withdrew from trials after miscarriage or the termination of pregnancy.

Discussion

Overall, the low to moderate statistical heterogeneity and consistency of effects across a range of outcomes supports the conclusion that low-dose aspirin is effective for preventing preeclampsia and related perinatal morbidity and mortality for individuals at increased risk for preeclampsia. The evidence is summarized by KQ in **Table 3**. This synthesis reported on 3 new studies not included in the previous USPSTF review, contributing to a more precise estimate of the association between aspirin and the prevention of perinatal mortality, indicating a range of effects spanning a 4% to 44% reduction in fetal and neonatal deaths. Otherwise, the new studies did not alter the previous findings of reduced risks of preeclampsia, preterm birth, and SGA/IUGR, or the previous null findings for reported bleeding harms. For individuals at increased risk of preeclampsia, daily low-dose aspirin therapy was associated with a lower risk of preeclampsia, preterm birth, SGA/IUGR, and perinatal mortality. Trial data derived from more than 25 000 pregnant individuals randomized to daily aspirin use did not reveal any serious harms. While very rare harms cannot be ruled out, large registry and cohort studies of potential harms not included in this review because aspirin exposure was for any indication, gestation, or dosage have not found clear evidence of teratogenic or other serious health effects.[51-56]

The results of this review are consistent with findings from other systematic reviews, including a recent Cochrane Collaboration review[57] and an older individual participant meta-analysis conducted by the Paris Collaborative Group (Paris IPD-MA) using data from trials published before 2006.[58-62] The Cochrane review included 77 trials conducted with 40 249 participants and their infants and incorporated available Paris IPD-MA data. The Cochrane review results were mostly consistent with the findings of this review despite differences in terms of included study design characteristics, preeclampsia risk levels, risk-of-bias exclusions, and statistical methods.

Subgroup comparisons using data included in this review did not identify consistent differences across outcomes in the magnitude of effects related to the timing of treatment initiation, the dosage of aspirin used, or personal characteristics such as smoking history, parity, and body mass index (BMI), nor were the approaches to assessing preeclampsia risk or the incidence of preeclampsia observed in the study population related to differences in effectiveness. Timing of aspirin initiation across the trials was broad, ranging from initiation in the first (11-12 weeks) to third (36-38 weeks) trimester, and there was not clear evidence that aspirin effectiveness for preeclampsia prevention varied based on timing of initiation, consistent with the Cochrane[57] and Paris IPD-MA reviews.[58,60] Trials also varied broadly in the dosage of aspirin used (50 mg/d to 150 mg/d), but dosage was not significantly associated with effectiveness in aggregate comparisons, also consistent with findings of other reviews.[57,58] At least 2 important questions related to aspirin dosage could not be addressed based on the available evidence included in this review. First, it is not clear whether women with a higher BMI require a higher dose of aspirin based on the trial evidence.[63] Second, only 2 of the included studies implemented dosages of 150 mg/d, and one of them (ASPRE, a new large trial) did not report postpartum hemorrhage outcomes, which limits the information available for assessing potential bleeding harms with a higher dosage.

The generalizability of the evidence across specific racial and ethnic populations is limited, given that a majority of participants in the included trials were White. This is troubling in light of the greater morbidity from preeclampsia experienced by Black women in the US and well-documented disparities in maternal health and birth outcomes arising from racism and systemic racial inequities.[6,14,64-67] These inequities also contribute to underrepresentation in research. Only 1 US trial of women at increased risk for developing preeclampsia (MFMU) enrolled substantial numbers of Black and Hispanic study participants,[40] and none of the included

Table 3. Summary of Evidence

No. of studies (study designs [No. of observations])	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of aspirin use on health outcomes					
18 RCTs (10 good quality, 8 fair quality [n = 15 908])	Aspirin was associated with a reduced risk of perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; I^2 = 0%), preterm birth (pooled RR, 0.80 [95% CI, 0.67-0.95]; I^2 = 49%), and SGA/IUGR (pooled RR, 0.82 [95% CI, 0.68-0.99]; I^2 = 41%) Limited subpopulation data, but within-trial comparison suggested greater effectiveness in nonsmokers	Reasonably consistent[a]; reasonably precise[b]	Small-study effects could not be ruled out for SGA/IUGR and preterm delivery Rare maternal health outcomes, such as eclampsia and maternal mortality, occurred too infrequently to estimate preventive effectiveness Subgroup effects limited by modest number of included studies and few within-trial subgroup analyses reported	Moderate for perinatal health benefits	Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d
KQ2: Benefits of aspirin use on preeclampsia prevention					
16 RCTs (10 good quality, 6 fair quality [n = 15 767])	Aspirin was associated with a statistically significant reduction in the risk of preeclampsia compared with placebo (pooled RR, 0.85 [95% CI, 0.75-0.95]; I^2 = 0%) No evidence of statistical difference in the magnitude of preeclampsia risk reduction related to the timing of treatment initiation, the dosage of aspirin used, or personal characteristics such as smoking history, parity, and BMI	Reasonably consistent evidence for aspirin benefit Reasonably precise 15% reduced risk of preeclampsia associated with daily aspirin use	Small-study effects could not be ruled out and might lead to some overestimation of pooled risk estimate Confounding of study size with other study and participant characteristics could influence subgroup comparisons Subgroup effects limited by modest number of included studies and few within-trial subgroup analyses reported	Moderate	Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d
KQ3: Harms of aspirin use					
21 RCTs (16 increased-risk and 5 average-risk populations; 14 good quality, 7 fair quality [n = 26 757]	Studies conducted among average-risk and increased-risk populations did not find any clear evidence of harms associated with daily aspirin use (<150 mg) taken during the second or third trimester of pregnancy No difference in harms by the dosage or timing of aspirin or for specific populations were identified in limited subgroup comparisons Bleeding harms were uncommon and showed null effects for differences in risk of postpartum hemorrhage (pooled RR, 1.03 [95% CI, 0.94-1.12]; I^2 = 0%; 11 studies) or fetal intracranial bleeding (pooled RR, 0.90 [95% CI, 0.51-1.57]; I^2 = 19%; 9 studies) were found The result for placental abruption (pooled RR, 1.15 [95% CI, 0.76-1.72]; I^2 = 25%; 13 studies) was also null Longer-term follow-up from 1 large trial found no difference in child developmental outcomes for aspirin-exposed vs placebo-exposed groups No differences were found within a limited set of studies reporting other rare perinatal harms	Reasonably consistent evidence of null effects for bleeding harms of daily aspirin, especially among pregnant individuals at increased preeclampsia risk Reasonably precise evidence for null effects, but less precise for especially rare harms	Reported harms were rare and not consistently reported across studies	Moderate for no difference in bleeding harms between groups, low for very rare or inconsistently reported harms[c]	Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d Harms from trials in average-risk and increased-risk populations

Abbreviations: BMI, body mass index; KQ, key question; RCT, randomized clinical trials; RR, risk ratio; SGA/IUGR, small-for-gestational age/intrauterine growth restriction.

[a] Direction and magnitude of effects within and across for important perinatal health outcomes, with low to moderate statistical heterogeneity.

[b] Confidence intervals did not cross null, including for rare outcomes such as perinatal mortality, for which where even small effects are clinically important.

[c] Postpartum hemorrhage greater than 1000 mL, longer-term developmental harms, congenital malformations.

studies enrolled significant numbers of other minority racial or ethnic groups. More recent evidence from a retrospective cohort study of births among Black and Hispanic individuals with a history of preeclampsia compared preeclampsia recurrence before and after the release of the 2014 USPSTF recommendation for aspirin prophylaxis.[68] Adjusted analyses showed a 30% reduced recurrence of preeclampsia after the release of the recommendation. The observational study design supports the applicability of trial evidence synthesized in this review to clinical settings serving diverse populations, but further research is needed to ensure that the benefits of aspirin prophylaxis are obtained and that implementation ensures this simple, effective intervention reaches all who might benefit.

Whether there are longer-term child and adult health benefits associated with aspirin prophylaxis is unclear. Only 1 included trial reported follow-up beyond the perinatal period, and it was limited to a subset of the children assessed at age 18 months.[36,69] While that study was reassuring with regard to the lack of developmental harms in early childhood, longer-term trial follow-up could evaluate whether aspirin prophylaxis reduces offspring risk of cardiovascular disease,[70,71] as well as risk for neurocognitive conditions such as attention-deficit/hyperactivity disorder,[72,73] autism spectrum disorder, epilepsy, intellectual disability, and vision or hearing loss.[74] No trials have yet reported on longer-term maternal outcomes. A number of cohort studies have found associations between preeclampsia and long-term cardiovascular health.[75,76] Estimates suggest a possible doubling or tripling of cardiovascular disease risk in women who have had preeclampsia during any pregnancy,[77,78] as well as an increased risk for early stroke (before age 60 years).[79,80] Further research could determine whether low-dose aspirin in pregnancy leads to longer-term reduction in risk of conditions associated with preeclampsia.[81]

Trial evidence from this review and findings from observational studies identify important risk factors for preeclampsia.[13,82,83] A common set of risk factors were cited in the previous USPSTF recommendation statement[84] and in the recent ACOG recommendation for aspirin to prevent preeclampsia.[85,86] The risk factors known to be independently associated with the highest likelihoods of developing preeclampsia include history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or type 2 diabetes, renal disease, and autoimmune diseases (eg, systemic lupus erythematous, antiphospholipid antibody syndrome). Risk factors more modestly associated with increased preeclampsia risk include maternal age older than 35 years, obesity (BMI >30 [calculated as weight in kilograms divided by height in meters squared]), and nulliparity and the presence of multiple risk factors heightens risk. While these risk factors and others[87-90] have been identified, evidence is limited with respect to best practices for identifying women at risk of preeclampsia that would benefit from aspirin prophylaxis.[91,92]

Of the 18 included trials among increased risk populations, 14 used multiple risk factors to identify study participants at risk for preeclampsia and the baseline characteristics of the study populations varied significantly, resulting in a broad range of preeclampsia incidence in the control groups (4%-30%). Studies that used clinical history risk factors in conjunction with clinical tests or imaging consistently recruited populations with high incidence of preeclampsia (18% and 23%),[30,46] but several studies using clinical risk factors alone achieved similarly high levels of preeclampsia incidence ranging from 8% to 20%.[34-36,39,40,42,45] Subgroup analyses did not show any differences in aspirin effectiveness when comparing studies that used clinical history risk factors alone vs those that incorporated clinical tests or imaging. Only 1 trial used a previously developed risk prediction model.[93] Reviews comparing the test performance attributes of available risk assessment models have found limitations in their readiness for clinical application, including significant differences in accuracy depending on the validation cohort used.[94,95] Further data would be needed to determine whether the use of a risk prediction model that requires multiple historical and physical measures to generate a risk estimate is superior to other clinical risk assessment approaches and whether widespread implementation into routine practice is feasible.[1,86,91,95,96] Implementation trials comparing different approaches to risk assessment and aspirin allocation in clinical settings would be particularly valuable.

Limitations

The evidence review has several limitations. First, the search was limited to English-language literature, and only trials conducted in settings with very high Human Development Index scores were included. Studies rated as poor quality were also excluded from analysis. However, other reviews without these exclusions have not found substantively different results.[57,58]

Second, there was evidence of small-study effects for some outcomes. Such effects can be observed when smaller studies with null or negative findings are absent from the literature (ie, publication bias) or due to reported and unreported differences between smaller and larger trials. Given the presence of small-study effects, it is possible that pooled effect sizes were overestimated for preeclampsia and preterm birth prevention; alternatively, the smaller effect sizes observed in the largest trials could be attributed to their common design features (eg, the 2 largest trials used 60-mg/d aspirin dosages). Third, confounding of study size and study design characteristics, as well as the number of studies available for analysis, limited the interpretation of aggregate subgroup comparisons since it was not possible to conduct multivariable meta-regression.

Fourth, across the trials, approaches to identify individuals at increased preeclampsia risk varied, as did inclusion and exclusion criteria, generating a broad range of absolute risks for the study outcomes. No studies reported head-to-head comparisons of different protocols or risk assessment strategies, and only 1 trial, which was underpowered for drawing conclusions, was designed to compare the effectiveness for different risk populations. Interaction tests for subgroup differences within trials were uncommon and, when available, did not generally identify differences in effectiveness by the factors examined. More research will be needed to determine the optimal aspirin protocol and identify key populations most likely to obtain preventive benefits.

Conclusions

Daily low-dose aspirin during pregnancy was associated with lower risks of serious perinatal outcomes for individuals at increased risk for preeclampsia, without evident harms.

ARTICLE INFORMATION

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Concept and design: Henderson, Vesco, Senger.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Henderson, Vesco, Senger.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Redmond.
Administrative, technical, or material support: Senger, Thomas, Redmond.
Supervision: Henderson.

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REFERENCES

1. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. *Obstet Gynecol*. 2019;133(1):1. doi:10.1097/AOG.0000000000003018

2. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25(4):391-403. doi:10.1016/j.bpobgyn.2011.01.006

3. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376(9741):631-644. doi:10.1016/S0140-6736(10)60279-6

4. Stevens W, Shih T, Incerti D, et al. Short-term costs of preeclampsia to the United States health care system. *Am J Obstet Gynecol*. 2017;217(3):237-248. doi:10.1016/j.ajog.2017.04.032

5. Pregnancy Mortality Surveillance System: causes of pregnancy-related death in the United States: 2011-2016. Centers for Disease Control and Prevention. Published 2019. Accessed July 15, 2021. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm

6. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011-2013. *Obstet Gynecol*. 2017;130(2):366-373. doi:10.1097/AOG.0000000000002114

7. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension*. 2008;51(4):970-975. doi:10.1161/HYPERTENSIONAHA.107.107607

8. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol*. 2012;36(1):56-59. doi:10.1053/j.semperi.2011.09.011

9. Mayrink J, Costa ML, Cecatti JG. Preeclampsia in 2018: revisiting concepts, physiopathology, and prediction. *ScientificWorldJournal*. 2018;2018:6268276. doi:10.1155/2018/6268276

10. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323-e333. doi:10.1016/S2214-109X(14)70227-X

11. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013;209(6):544.e1-544.e12. doi:10.1016/j.ajog.2013.08.019

12. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. *Am J Obstet Gynecol*. 2006;195(6):1557-1563. doi:10.1016/j.ajog.2006.05.021

13. Fingar KR, Mabry-Hernandez I, Ngo-Metzger Q, Wolff T, Steiner CA, Elixhauser A. *Delivery Hospitalizations Involving Preeclampsia and Eclampsia, 2005–2014*. Agency for Healthcare Research and Quality; 2017. Statistical Brief 222.

14. Gyamfi-Bannerman C, Pandita A, Miller EC, et al. Preeclampsia outcomes at delivery and race. *J Matern Fetal Neonatal Med*. 2020;33(21):3619-3626.

15. US Preventive Services Task Force. Final recommendation statement: low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: preventive medication. Agency for Health Care Research and Quality. Published 2014. Accessed May 14, 2021. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/low-dose-aspirin-use-for-the-prevention-of-morbidity-and-mortality-from-preeclampsia-preventive-medication

16. US Preventive Services Task Force. *USPSTF Procedure Manual*. Agency for Healthcare Research and Quality; 2015.

17. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. *Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: An Evidence Update for the US Preventive Services Task Force. Evidence Synthesis No. 205*. Agency for Healthcare Research and Quality; 2021. AHRQ publication 21-05274-EF-1.

18. Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the US Preventive Services Task Force. *Ann Intern Med*. 2014;160(10):695-703. doi:10.7326/M13-2844

19. United Nations Development Programme. *Human Development Report*. United Nations; 2016.

20. Raudenbush SW. Analyzing effect sizes: random-effects models. In: Cooper H, Hedges LV, Valentine JC, eds. *The Handbook of Research Synthesis and Meta-analysis*. 2nd ed. Russell Sage Foundation; 2009:296-314.

21. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22(17):2693-2710. doi:10.1002/sim.1482

22. Veroniki AA, Jackson D, Bender R, et al. Methods to calculate uncertainty in the estimated overall effect size from a random-effects meta-analysis. *Res Synth Methods*. 2019;10(1):23-43. doi:10.1002/jrsm.1319

23. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27(5):335-371. doi:10.1016/S0033-0620(85)80003-7

24. Cheng J, Pullenayegum E, Marshall JK, Iorio A, Thabane L. Impact of including or excluding both-armed zero-event studies on using standard meta-analysis methods for rare event outcome: a simulation study. *BMJ Open*. 2016;6(8):e010983. doi:10.1136/bmjopen-2015-010983

25. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA*. 2006;295(6):676-680. doi:10.1001/jama.295.6.676

26. Sterne JAC, Harbord RM. Funnel plots in meta-analysis. *Stata J*. 2004;4(2):127-141. doi:10.1177/1536867X0400400204

27. Jin Z-C, Zhou X-H, He J. Statistical methods for dealing with publication bias in meta-analysis. *Stat Med*. 2015;34(2):343-360. doi:10.1002/sim.6342

28. Wallenburg HC, Dekker GA, Makovitz JW, Rotmans P. Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae. *Lancet*. 1986;1(8471):1-3. doi:10.1016/S0140-6736(86)91891-X

29. Benigni A, Gregorini G, Frusca T, et al. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. *N Engl J Med*. 1989;321(6):357-362. doi:10.1056/NEJM198908103210604

30. Schiff E, Peleg E, Goldenberg M, et al. The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies. *N Engl J Med*. 1989;321(6):351-356. doi:10.1056/NEJM198908103210603

31. McParland P, Pearce JM, Chamberlain GV. Doppler ultrasound and aspirin in recognition and prevention of pregnancy-induced hypertension. *Lancet*. 1990;335(8705):1552-1555. doi:10.1016/0140-6736(90)91377-M

32. Hauth JC, Goldenberg RL, Parker CR Jr, et al. Low-dose aspirin therapy to prevent preeclampsia. *Am J Obstet Gynecol*. 1993;168(4):1083-1091. doi:10.1016/0002-9378(93)90351-I

33. Sibai BM, Caritis SN, Thom E, et al; National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med*. 1993;329(17):1213-1218. doi:10.1056/NEJM199310213291701

34. Viinikka L, Hartikainen-Sorri AL, Lumme R, Hiilesmaa V, Ylikorkala O. Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacyclin-thromboxane balance in mother and newborn. *Br J Obstet Gynaecol*. 1993;100(9):809-815. doi:10.1111/j.1471-0528.1993.tb14304.x

35. Caspi E, Raziel A, Sherman D, Arieli S, Bukovski I, Weinraub Z. Prevention of pregnancy-induced hypertension in twins by early administration of low-dose aspirin: a preliminary report. *Am J Reprod Immunol*. 1994;31(1):19-24. doi:10.1111/j.1600-0897.1994.tb00842.x

36. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet*. 1994;343(8898):619-629. doi:10.1016/S0140-6736(94)92633-6

37. Davies NJ, Gazvani MR, Farquharson RG, Walkinshaw SA. Low-dose aspirin in the prevention of hypertensive disorders of pregnancy in relatively low-risk nulliparous women. *Hypertens Pregnancy*. 1995;14(1):49-55. doi:10.3109/10641959509058050

38. Gallery EDM, Ross MR, Hawkins M, Leslie G, Györy AZ. Low-dose aspirin in high-risk pregnancy? *Hypertens Pregnancy*. 1997;16(2):229-238. doi:10.3109/10641959709031640

39. Hermida RC, Ayala DE, Iglesias M, et al. Time-dependent effects of low-dose aspirin administration on blood pressure in pregnant women. *Hypertension*. 1997;30(3, pt 2):589-595. doi:10.1161/01.hyp.30.3.589

40. Caritis S, Sibai B, Hauth J, et al; National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Low-dose aspirin to prevent preeclampsia in women at high risk. *N Engl J Med*. 1998;338(11):701-705. doi:10.1056/NEJM199803123381101

41. Rotchell YE, Cruickshank JK, Gay MP, et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol*. 1998;105(3):286-292. doi:10.1111/j.1471-0528.1998.tb10088.x

42. Grab D, Paulus WE, Erdmann M, et al. Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound Obstet Gynecol*. 2000;15(1):19-27. doi:10.1046/j.1469-0705.2000.00009.x

43. Subtil D, Goeusse P, Puech F, et al; Essai Régional Aspirine Mère-Enfant (ERASME) Collaborative Group. Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (part 1). *BJOG*. 2003;110(5):475-484.

44. Yu CK, Papageorghiou AT, Parra M, Palma Dias R, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Randomized controlled trial using low-dose aspirin in the prevention of pre-eclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol*. 2003;22(3):233-239. doi:10.1002/uog.218

45. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int*. 2013;30(1-2):260-279. doi:10.3109/07420528.2012.717455

46. Villa PM, Kajantie E, Räikkönen K, et al; PREDO Study Group. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO trial and a meta-analysis of randomised trials. *BJOG*. 2013;120(1):64-74. doi:10.1111/j.1471-0528.2012.03493.x

47. Mone F, Mulcahy C, McParland P, et al. *T*rial of feasibility and acceptability of routine low-dose aspirin versus *E*arly *S*creening *T*est indicated aspirin for pre-eclampsia prevention (*TEST* study): a multicentre randomised controlled trial. *BMJ Open*. 2018;8(7):e022056. doi:10.1136/bmjopen-2018-022056

48. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377(7):613-622. doi:10.1056/NEJMoa1704559

49. Scazzocchio E, Oros D, Diaz D, et al. Impact of aspirin on trophoblastic invasion in women with abnormal uterine artery Doppler at 11-14 weeks: a randomized controlled study. *Ultrasound Obstet Gynecol*. 2017;49(4):435-441. doi:10.1002/uog.17351

50. Morris JM, Fay RA, Ellwood DA, Cook CM, Devonald KJ. A randomized controlled trial of aspirin in patients with abnormal uterine artery blood flow. *Obstet Gynecol*. 1996;87(1):74-78. doi:10.1016/0029-7844(95)00340-1

51. Nakhai-Pour HR, Bérard A. Major malformations after first trimester exposure to aspirin and NSAIDs. *Expert Rev Clin Pharmacol*. 2008;1(5):605-616. doi:10.1586/17512433.1.5.605

52. Coomarasamy A, Braunholtz D, Song F, Taylor R, Khan KS. Individualising use of aspirin to prevent pre-eclampsia: a framework for clinical decision making. *BJOG*. 2003;110(10):882-888. doi:10.1111/j.1471-0528.2003.03002.x

53. Hernandez RK, Werler MM, Romitti P, Sun L, Anderka M; National Birth Defects Prevention Study. Nonsteroidal antiinflammatory drug use among women and the risk of birth defects. *Am J Obstet Gynecol*. 2012;206(3):228.e1-228.e8. doi:10.1016/j.ajog.2011.11.019

54. Given JE, Loane M, Garne E, et al. Gastroschisis in Europe—a case-malformed-control study of medication and maternal illness during pregnancy as risk factors. *Paediatr Perinat Epidemiol*. 2017;31(6):549-559. doi:10.1111/ppe.12401

55. Jensen MS, Rebordosa C, Thulstrup AM, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology*. 2010;21(6):779-785. doi:10.1097/EDE.0b013e3181f20bed

56. Keim SA, Klebanoff MA. Aspirin use and miscarriage risk. *Epidemiology*. 2006;17(4):435-439. doi:10.1097/01.ede.0000221693.72971.b3

57. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2019;2019(10):CD004659. doi:10.1002/14651858.CD004659.pub3

58. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA; PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet*. 2007;369(9575):1791-1798. doi:10.1016/S0140-6736(07)60712-0

59. Stewart GB, Altman DG, Askie LM, Duley L, Simmonds MC, Stewart LA. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. *PLoS One*. 2012;7(10):e46042. doi:10.1371/journal.pone.0046042

60. Meher S, Duley L, Hunter K, Askie L. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. *Am J Obstet Gynecol*. 2017;216(2):121-128. doi:10.1016/j.ajog.2016.10.016

61. van Vliet EOG, Askie LA, Mol BWJ, Oudijk MA. Antiplatelet agents and the prevention of spontaneous preterm birth: a systematic review and meta-analysis. *Obstet Gynecol*. 2017;129(2):327-336. doi:10.1097/AOG.0000000000001848

62. Seidler AL, Askie L, Ray JG. Optimal aspirin dosing for preeclampsia prevention. *Am J Obstet Gynecol*. 2018;219(1):117-118. doi:10.1016/j.ajog.2018.03.018

63. Finneran MM, Gonzalez-Brown VM, Smith DD, Landon MB, Rood KM. Obesity and laboratory aspirin resistance in high-risk pregnant women treated with low-dose aspirin. *Am J Obstet Gynecol*. 2019;220(4):385.e1-385.e6. doi:10.1016/j.ajog.2019.01.222

64. Ross KM, Dunkel Schetter C, McLemore MR, et al. Socioeconomic status, preeclampsia risk and gestational length in black and white women. *J Racial Ethn Health Disparities*. 2019;6(6):1182-1191. doi:10.1007/s40615-019-00619-3

65. Shahul S, Tung A, Minhaj M, et al. Racial disparities in comorbidities, complications, and maternal and fetal outcomes in women with preeclampsia/eclampsia. *Hypertens Pregnancy*. 2015;34(4):506-515. doi:10.3109/10641955.2015.1090581

66. Petersen EE, Davis NL, Goodman D, et al. Racial/ethnic disparities in pregnancy-related deaths—United States, 2007-2016. *MMWR Morb Mortal Wkly Rep*. 2019;68(35):762-765. doi:10.15585/mmwr.mm6835a3

67. Howell EA. Reducing disparities in severe maternal morbidity and mortality. *Clin Obstet Gynecol*. 2018;61(2):387-399. doi:10.1097/GRF.0000000000000349

68. Tolcher MC, Chu DM, Hollier LM, et al. Impact of USPSTF recommendations for aspirin for prevention of recurrent preeclampsia. *Am J Obstet Gynecol*. 2017;217(3):365.e1-365.e8. doi:10.1016/j.ajog.2017.04.035

69. Clasp Collaborative Group. Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. *Br J Obstet Gynaecol*. 1995;102(11):861-868. doi:10.1111/j.1471-0528.1995.tb10872.x

70. Jayet PY, Rimoldi SF, Stuber T, et al. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. *Circulation*. 2010;122(5):488-494. doi:10.1161/CIRCULATIONAHA.110.941203

71. Nahum Sacks K, Friger M, Shoham-Vardi I, et al. Prenatal exposure to preeclampsia as an independent risk factor for long-term cardiovascular morbidity of the offspring. *Pregnancy Hypertens*. 2018;13:181-186. doi:10.1016/j.preghy.2018.06.013

72. Maher GM, Dalman C, O'Keeffe GW, et al. Association between preeclampsia and attention-deficit hyperactivity disorder: a population-based and sibling-matched cohort study. *Acta Psychiatr Scand*. 2020;142(4):275-283. doi:10.1111/acps.13162

73. Nahum Sacks K, Friger M, Shoham-Vardi I, et al. Long-term neuropsychiatric morbidity in children exposed prenatally to preeclampsia. *Early Hum Dev*. 2019;130:96-100. doi:10.1016/j.earlhumdev.2019.01.016

74. Sun BZ, Moster D, Harmon QE, Wilcox AJ. Association of preeclampsia in term births with neurodevelopmental disorders in offspring. *JAMA Psychiatry*. 2020;77(8):823-829. doi:10.1001/jamapsychiatry.2020.0306

75. Davis EF, Lazdam M, Lewandowski AJ, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics*. 2012;129(6):e1552-e1561. doi:10.1542/peds.2011-3093

76. Valdiviezo C, Garovic VD, Ouyang P. Preeclampsia and hypertensive disease in pregnancy: their contributions to cardiovascular risk. *Clin Cardiol*. 2012;35(3):160-165. doi:10.1002/clc.21965

77. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335(7627):974. doi:10.1136/bmj.39335.385301.BE

78. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53(6):944-951. doi:10.1161/HYPERTENSIONAHA.109.130765

79. Miller EC, Boehme AK, Moon YP, et al. Preeclampsia and early stroke incidence in the California Teachers Study. *Stroke*. 2018;49(suppl 1):A174. doi:10.1161/str.49.suppl_1.174

80. Lederer M, Wong A, Diego D, Nguyen D, Verma U, Chaturvedi S. Tracking the development of cerebrovascular risk factors following pregnancy with preeclampsia. *J Stroke Cerebrovasc Dis*. 2020;29(6):104720. doi:10.1016/j.jstrokecerebrovasdis.2020.104720

81. Bergman L, Torres-Vergara P, Penny J, et al. Investigating maternal brain alterations in preeclampsia: the need for a multidisciplinary effort. *Curr Hypertens Rep*. 2019;21(9):72. doi:10.1007/s11906-019-0977-0

82. Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ*. 2016;353:i1753. doi:10.1136/bmj.i1753

83. Ghosh G, Grewal J, Männistö T, et al. Racial/ethnic differences in pregnancy-related hypertensive disease in nulliparous women. *Ethn Dis*. 2014;24(3):283-289.

84. LeFevre ML; US Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161(11):819-826. doi:10.7326/M14-1884

85. Bailey B, Euser AG, Bol KA, Julian CG, Moore LG. High-altitude residence alters blood-pressure course and increases hypertensive disorders of pregnancy. *J Matern Fetal Neonatal Med*. 2020;1-8. doi:10.1080/14767058.2020.1745181

86. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 743: low-dose aspirin use during pregnancy. *Obstet Gynecol*. 2018;132(1):e44-e52. doi:10.1097/AOG.0000000000002708

87. Bai W, Li Y, Niu Y, et al. Association between ambient air pollution and pregnancy complications: a systematic review and meta-analysis of cohort studies. *Environ Res*. 2020;185:109471. doi:10.1016/j.envres.2020.109471

88. Wilson DL, Howard ME, Fung AM, et al. The presence of coexisting sleep-disordered breathing among women with hypertensive disorders of pregnancy does not worsen perinatal outcome. *PLoS One*. 2020;15(2):e0229568. doi:10.1371/journal.pone.0229568

89. Li L, Zhao K, Hua J, Li S. Association between sleep-disordered breathing during pregnancy and maternal and fetal outcomes: an updated systematic review and meta-analysis. *Front Neurol*. 2018;9:91. doi:10.3389/fneur.2018.00091

90. Aukes AM, Yurtsever FN, Boutin A, Visser MC, de Groot CJM. Associations between migraine and adverse pregnancy outcomes: systematic review and meta-analysis. *Obstet Gynecol Surv*. 2019;74(12):738-748. doi:10.1097/OGX.0000000000000738

91. Al-Rubaie Z, Askie LM, Ray JG, Hudson HM, Lord SJ. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. *BJOG*. 2016;123(9):1441-1452. doi:10.1111/1471-0528.14029

92. Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol*. 2018;51(6):743-750. doi:10.1002/uog.19039

93. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther*. 2013;33(1):8-15. doi:10.1159/000341264

94. Allen RE, Zamora J, Arroyo-Manzano D, et al. External validation of preexisting first trimester preeclampsia prediction models. *Eur J Obstet Gynecol Reprod Biol*. 2017;217:119-125. doi:10.1016/j.ejogrb.2017.08.031

95. Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia screening: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;317(16):1668-1683. doi:10.1001/jama.2016.18315

96. Roberts JM, Himes KP. Pre-eclampsia: screening and aspirin therapy for prevention of pre-eclampsia. *Nat Rev Nephrol*. 2017;13(10):602-604. doi:10.1038/nrneph.2017.121