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Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality

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Structured Abstract

Objective: We conducted this review to support the United States Preventive Services Task Force (USPSTF) in updating its 2014 recommendation on daily low dose aspirin use during pregnancy for individuals at increased risk for preeclampsia. We systematically reviewed updated evidence on the effectiveness and potential harms of daily aspirin use in pregnancy to prevent morbidity and mortality associated with preeclampsia.

Data Sources: We performed comprehensive searches of MEDLINE, PubMed (publisher-supplied only), Embase, and the Cochrane Collaboration Registry of Controlled Trials for studies published between January 2013 and July 2019. A research librarian developed and executed the search strategy. Studies included in the prior review to support the 2014 recommendation and studies referenced in recently published reviews were also considered for inclusion.

Study Selection: We reviewed 3749 newly identified abstracts and 183 articles against prespecified inclusion criteria developed for the current review. Studies were included if they evaluated daily treatment during pregnancy with aspirin not combined with any other medication at a dosage of ≥50mg daily compared with placebo or no treatment. Included studies reported incidence of preeclampsia or serious maternal, perinatal, and longer-term health outcomes. For studies evaluating aspirin effectiveness, eligible study designs included randomized controlled trials (RCTs) and individual participant data meta-analyses that enrolled pregnant persons who were at increased risk for preeclampsia based on personal sociodemographic characteristics, medical history, diagnostic measurements or assays, or risk prediction models. For studies evaluating harms of aspirin use, the study design criteria were expanded to include observational studies and trials conducted in average-risk populations.

Data Analysis: Eligible studies that were determined to have high risk of bias were excluded for poor quality according to standard USPSTF procedures. Descriptions of study populations, study design characteristics, and outcomes were developed for all included studies. The most consistently reported health outcomes were analyzed using random effects meta-analytic model to calculate pooled intervention effects and subgroup comparisons were tested with meta-regression tests for interaction. We examined whether the results were influenced by small-study effects using the Peters test and visual inspection of forest plots.

Results: Twenty-three studies (33 articles) met our inclusion criteria. Four studies included in the previous review (including two observational studies) were not included and four new trials were added. We included 18 trials evaluating aspirin effectiveness in individuals at increased risk for preeclampsia; all but one used a matching placebo comparator. Dosages of aspirin ranged from 50-150 mg per day, usually starting in the second or third trimester and continuing until delivery or near term. These interventions were associated with reduced risks 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 small for gestational age/intrauterine growth restriction (SGA/IUGR) (pooled RR 0.82 [95% CI 0.68, 0.99], I^2 41%). There was also a statistically significant reduction in the risk of preeclampsia (pooled RR, 0.85 [95% CI, 0.75 to 0.95], I^2 0%). Rare maternal health outcomes, such as eclampsia and maternal mortality, occurred too infrequently to estimate preventive effectiveness. In meta-analytic subgroup comparisons, we found no consistent

evidence for effect differences related to intervention or population characteristics such as the timing of treatment initiation, the dosage of aspirin used, or participant characteristics. There was evidence of small-study effects for several of the pooled health outcomes.

Studies in average and increased-risk populations did not provide any clear evidence of harms associated with daily aspirin use (<150mg) taken during the second or third trimester of pregnancy, and there was no evidence of differences in harms by aspirin dosage or timing, or for specific populations identified in limited subgroup comparisons. Bleeding related harms were uncommon; our analyses showed null effects for differences in risk of postpartum hemorrhage (pooled RR 1.03, [95% CI, 0.94, 1.12], I^2 0%, k=9), or intracranial fetal bleeding (pooled RR, 0.90 [95% CI, 0.51, 1.57]; I^2 19%, k=6) between intervention and control groups. There was also no difference in rates of placental abruption (pooled RR, 1.15 [95% CI, 0.76, 1.72], I^2 25%, k=10). Longer-term followup from one large trial found no differences in child developmental outcomes between aspirin and placebo exposed groups. No differences were found in a limited set of studies reporting other rare perinatal harms.

Limitations: Our search was limited to English-language literature and trials conducted in settings other than very high Human Development Index settings were excluded. Large trials conducted in other settings could provide additional relevant information, but evidence from other reviews without this exclusion do not find substantively different results. The meta-analysis results for some outcomes were limited by low numbers of included studies and very few events. Conservative approaches to estimation of pooled effects and testing of subgroup comparisons were used but cannot fully address some limitations in the data. The two largest studies used the same low aspirin dosage (60mg) and enrolled a majority of participants after 16 weeks of gestation and small-study effects cannot be entirely disentangled from other design and population features of the included studies. Despite inequities in preeclampsia rates by race and ethnicity in the United States, most trials enrolled predominantly White populations. Evidence also was lacking on potential longer-term health consequences of low dose aspirin exposure during pregnancy.

Conclusions: Daily aspirin use in pregnancy for individuals at increased risk for preeclampsia consistently led to beneficial effects on perinatal mortality, preterm birth, fetal growth restriction, and preeclampsia diagnosis across a clinically heterogeneous set of trials. A large body of trial evidence shows no clear signal of serious harms associated with daily low dose aspirin use in the second and third trimesters of pregnancy. Further research from pragmatic and comparative effectiveness trials is needed to identify the best way to identify patients at increased preeclampsia risk who are most likely to benefit from aspirin use, and to obtain greater clarity on the optimal regimen. Finally, the benefits of aspirin prophylaxis may not always reach those at risk, especially among populations with limited access to high quality prenatal care. Implementing strategies that promote equitable access to this intervention could help address preeclampsia health inequities, especially those observed for Black women in the United States.

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Condition Background

Condition Definition

Preeclampsia is a pregnancy-specific disease that occurs after the 20th week of pregnancy and is defined as the new onset of hypertension (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg, on two occasions at least 4 hours apart) in a person with previously normal blood pressure, together with additional specified signs or symptoms.[1, 2] Although preeclampsia was historically diagnosed as hypertension accompanied by new onset proteinuria (300 mg/dL of protein in a 24-hour urine collection or a protein-to-creatinine ratio of 0.30 or more), in 2013 the American College of Obstetricians and Gynecologists (ACOG) revised the diagnostic criteria such that proteinuria is no longer requisite for diagnosis. In the absence of proteinuria, preeclampsia is diagnosed when hypertension is accompanied by any of the following signs or symptoms: thrombocytopenia; impaired liver function as indicated by elevated blood concentrations of liver enzymes and severe persistent right upper quadrant or epigastric pain unresponsive to medication; renal insufficiency; pulmonary edema; new-onset headache unresponsive to medication; or visual disturbances.[1] The presence of any of these systemic signs or symptoms, or of severe hypertension (systolic ≥160 mm Hg or diastolic >110mmHg), also define the clinical designation of "preeclampsia with severe features."[1]

Gestational hypertension alone (i.e. new onset hypertension after 20 weeks of gestation that is not accompanied by the additional signs and symptoms that define preeclampsia), is also associated with adverse pregnancy outcomes and an increased risk for future chronic hypertension and cardiovascular disease.[1] Gestational hypertension is defined as new onset of elevated blood pressure (SBP of 140 mm Hg or more or DBP of 90 mm Hg or more, on two occasions at least 4 hours apart) after 20 weeks gestation in the absence of proteinuria or other signs or symptoms of preeclampsia.[1] Gestational hypertension requires enhanced surveillance as up to 50 percent of women develop proteinuria or other signs of preeclampsia, and progression is more likely if hypertension arises prior to 32 weeks of gestation.[1] Chronic hypertension with superimposed preeclampsia is diagnosed when there is new onset of proteinuria beyond 20 weeks in a woman with chronic hypertension but without prior proteinuria, or sudden onset of the following: substantial sustained increases in protein excretion, exacerbation of hypertension with need to escalate antihypertensive medication dose, or manifestation of systemic signs and symptoms associated with preeclampsia.

Preeclampsia can remain stable until delivery, but occasionally can quickly and unpredictably take a more serious turn. Severe hypertension; eclampsia; hemolysis, elevated liver enzymes, and low platelet counts (HELLP syndrome); and other organ or systemic complications can lead to maternal or fetal injury and death.[2, 3] There is some variation in the diagnostic criteria for HELLP syndrome, but the following are widely agreed upon: lactate dehydrogenase elevated to 600 IU/L or more, aspartate aminotransferase and alanine aminotransferase elevated more than twice the upper limit of normal, and platelet counts less than 100 x 10^9/L.[1, 4,9] The majority of HELLP

syndrome cases are seen in the third trimester, but about a third of cases present or progress postpartum. The primary symptoms of HELLP syndrome include right upper quadrant pain and generalized malaise, with nausea and vomiting seen in approximately half of cases.

Prevalence and Burden

Preeclampsia and eclampsia are the second and third most common causes of maternal morbidity and mortality worldwide, respectively.[5-7] Access to standard medical care has been shown to greatly improve health outcomes, as demonstrated by higher proportions of maternal mortality attributed to hypertensive disorders of pregnancy in lower income countries.[8]

In the United States, preeclampsia occurs in about 1 in 25 pregnancies that continue beyond 20 weeks of gestation. In a large retrospective cohort analysis of nearly 37 million deliveries (n=36,985,729) in the United States from 2006 to 2015, 3.8 percent received a diagnosis of preeclampsia. Severe preeclampsia increased as a proportion of preeclampsia cases over the study period, as did superimposed preeclampsia (preeclampsia arising in women with pre-existing chronic hypertension).[9] A rising trend in the proportion of hospital deliveries in the US complicated by preeclampsia and/or preeclampsia is evident from Healthcare Cost and Utilization Project data on all hospital deliveries in the United States, a 21 percent increase from 38.4 per 1,000 deliveries in 2005 to 46.6 per 1,000 deliveries in 2014).[10] Of over 175,000 deliveries with preeclampsia estimated in 2014 from these data, over one third (37%) were categorized as severe preeclampsia, 15 percent were cases among individuals with preexisting hypertension, and 1 percent resulted in eclampsia.[10]

In the United States, the risk of preeclampsia and of serious morbidity and mortality from the condition is greatest for Black women.[10, 11] Rates of preeclampsia are more than twice as high among Black women and more likely to manifest as severe disease. National estimates have shown that fewer than half of White women had severe preeclampsia whereas nearly two-thirds of cases among Black women were severe.[10, 12] Consequently, overall maternal mortality ratios and the contribution of preeclampsia/eclampsia to maternal mortality are higher for Black women.[13] Disparities in overall health, chronic health conditions, health care access, psychosocial stress, and systemic racial biases in health care are thought to contribute to the greater risk and worse outcomes of preeclampsia for Black women.[12, 14]

From 2011-2016, hypertensive disorders of pregnancy were responsible for 6.9 percent of pregnancy-related deaths in the United States.[13, 15] Significant maternal morbidities associated with preeclampsia include cerebrovascular bleeding, retinal detachment, and organ damage and failure complications from HELLP syndrome.[16, 17] Eclamptic seizures occur in approximately 1 to 2 percent of preeclampsia cases, and can lead to death or serious complications such as brain damage, aspiration pneumonia, pulmonary edema, placental abruption, disseminated coagulopathy, acute renal failure, cardiopulmonary arrest, and coma.[5] Serious morbidity is more common than mortality; cohort data from obstetric patients attending 25 U.S.-based medical centers encompassing the Maternal-Fetal Medicine Units Network from 2008 to 2011 indicated that at least 21 percent of severe maternal morbidity (i.e., requiring surgical intervention, intubation, blood transfusion, or intensive care unit admission or diagnosed failure of at least one organ system) was attributable to hypertensive disorders of pregnancy.[18] The serious threat to

maternal health associated with preeclampsia contributes to clinical decision-making related to the timing of delivery and other interventions to reduce maternal risk.

Preeclampsia increases the risk of adverse fetal, neonatal, and child health outcomes. These risks include intrauterine growth restriction, small for gestational age, low birth weight, preterm birth, placental abruption, stillbirth, and neonatal death.[2] The majority of preeclampsia cases occur after 34 weeks, but perinatal morbidity and mortality are greatest for early onset disease.[19] Due to the fact that the only effective treatment for preeclampsia is delivery, the condition is a leading cause of medically induced preterm birth and low birth weight. It has been estimated that preeclampsia contributes to 6 percent of preterm births and 19 percent of medically indicated preterm births.[20] Infants born before term (<37 weeks of gestation) are at increased risk of morbidity and mortality, with risks rising dramatically with earlier delivery.

There is also growing evidence that having preeclampsia is associated with increased risk of maternal chronic hypertension and cardiovascular disease later in life, including congestive heart failure,[21] myocardial infarction, and stroke.[22] The risk appears to be greatest among women who have experienced preeclampsia in more than one pregnancy,[23] required preterm delivery, or had a pregnancy complicated by fetal growth restriction.[24] Other data suggest that having had any hypertensive disorder of pregnancy may also be associated with long-term cardiovascular health risk.[25, 26] It is not yet clear whether this is due to common underlying risk factors for cardiovascular conditions across the life span, or whether the occurrence of a hypertensive disorder in pregnancy alters risk and predisposes one to future cardiovascular disease.

Etiology and Natural History

The underlying cause of preeclampsia is not fully understood, however, the placenta is thought to play a central role in its development. Preeclampsia can occur even in pregnancies without fetal development (e.g. hydatidiform mole) and it does not appear to regress until the placenta is removed or resorbed.[27] While delivery is important for curing the disease, its manifestations may take days or weeks postpartum to resolve, resulting in some cases presenting or being diagnosed in the postpartum period. The development of preeclampsia is usually presented as involving at least two stages—the placental stage and the maternal stage. The placental stage involves abnormal placentation, which contributes to early-onset preeclampsia (delivery<34 weeks gestation), and/or placental microvillus overcrowding, which develops with advancing pregnancy and is thought to contribute to late-onset of preeclampsia.[28, 29] The consequence of these changes is reduced placental perfusion, leading to hypoxia, placental ischemia, oxidative stress, and ultimately the release of damaging factors (i.e., cellular debris, oxidized lipids, antiangiogenic factors, soluble endoglin) into the maternal blood stream.[27, 30-32] The second, "maternal" stage involves the development of systemic maternal sequelae resulting from placental dysfunction.[27, 30] Placental damage leads to activation of platelets and the maternal clotting system,[33] and a systemic inflammatory response.[28] Changes in the renin-angiotensin-aldosterone system and increased sensitivity of blood vessels to contractile agents result in vasoconstriction.[30] Reduced perfusion, resulting from vasoconstriction, vascular occlusion by microthrombi, reduced vascular volume from leaking of fluid from the intravascular compartment, and vascular inflammation affect virtually every maternal organ in a women with

preeclampsia.[27, 29] Placental perfusion abnormalities may also affect the fetus, leading to increased-risk of fetal growth restriction among women with preeclampsia.

Risk Factors

It is not clear why abnormal placentation occurs and preeclampsia develops, but the process may be influenced by maternal genetic, environmental, and immunologic factors.[27, 30, 34] In addition, the observation of heightened risk of preeclampsia during first pregnancies and in women who undergo in vitro fertilization with donor eggs has led to numerous investigations regarding the potential interaction of maternal physiology with fetal/paternal genes .[2, 35]

Factors associated with risk of preeclampsia can be classified into those obtained by clinical history, clinical exam, laboratory tests, and imaging. Patient characteristics associated with increased risk for preeclampsia include high pre-pregnancy BMI; nulliparity; [10, 36]maternal age greater than 35 years; family history of preeclampsia, specifically a mother or sister with preeclampsia; and family history of early-onset cardiovascular disease. In addition, Black race has been identified as risk marker because Black individuals have higher rates of preeclampsia and are at risk for more serious complications.[10, 36] These inequities have arisen from historical and present-day manifestations of racism and structural disadvantage that influence environmental exposures, access to health resources, and overall health status.[37] Current or past medical conditions that increase the risk of preeclampsia include preeclampsia, placental abruption, or stillbirth in a prior pregnancy; the presence of multifetal gestation; autoimmune disease, such as systemic lupus erythematous or antiphospholipid antibody syndrome; pregestational diabetes mellitus; chronic hypertension; renal disease; and conception via assisted reproductive technology.[38] Rates of preeclampsia associated with different risk factors vary. The medical history risk factors described above are more strongly associated with incidence of preeclampsia than patient characteristics such as nulliparity and maternal age, doubling or tripling the risk of developing preeclampsia. The presence of multiple risk factors, whether personal characteristics or medical history risk factors, further heightens risk for the condition. Individuals at lowest risk are those who have previously had an uncomplicated term pregnancy and do not have any conditions or circumstances known to increase risk.

Various maternal measures, including lab tests, blood pressure response to a stimulus, and ultrasound assessments of uterine artery blood flow, have been evaluated as means to identify women at increased risk of developing preeclampsia. In addition, several models have been developed that aim to identify women who are at risk of developing preeclampsia. Many of these models include variables for medical history, patient characteristics, blood serum biomarkers (e.g., serum placental growth factor), mean arterial pressure (MAP), and ultrasound readings (e.g., Doppler uterine artery pulsatility index). The most extensively researched of these are various iterations of the Fetal Medicine Foundation (FMF) model; a recent publication provides the most complete development and validation evidence to date.[39] As in earlier studies of the model, performance was best for prediction of the more rare cases of preeclampsia requiring delivery early in pregnancy (<34 weeks). Evidence to support clinical application of available risk prediction models is limited, as there are very few external validation and implementation studies, and it is unclear whether risk prediction models are superior to risk assessment based on clinical history taking.[40]

Treatment Approaches

The only curative treatment for preeclampsia is delivery of the placenta. Current recommendations for delivery of patients with preeclampsia consider the risks and benefits both to the mother and the fetus. For women with gestational hypertension and preeclampsia without severe features, delivery is recommended when the patient reaches 37 0/7 weeks of gestation. For preeclampsia with severe features, delivery is recommended at 34 0/7 weeks of gestation, or at the time it occurs if after 34 0/7 weeks. Given the serious morbidity associated with HELLP syndrome, delivery is recommended regardless of gestational age at which it arises. Similarly, women with eclampsia should be delivered in a timely manner once the patient is stabilized. Close antenatal surveillance of women with gestational hypertension or preeclampsia without severe features arising prior to 37 weeks of gestation is required to assess for worsening disease or fetal compromise that might require more expedient delivery.[1]

Secondary prevention measures to avoid serious complications from preeclampsia include administration of antihypertensive medications to prevent stroke and administration of magnesium sulfate to prevent eclamptic seizures.[1, 41-44]

Preeclampsia Prevention

Interventions aimed at reducing the risk of preeclampsia have focused on several of the pathways potentially involved in its development, including vasoconstriction and platelet aggregation as well as metabolic abnormalities and nutritional deficiencies such as inadequate dietary calcium.[45] In a systematic review of 27 randomized trials of calcium supplementation for the prevention of preeclampsia, high-dose calcium supplementation (≥1 g/day) was shown to reduce the risk of preeclampsia and preterm birth, among women with a history of a low calcium diet (<900 mg/day).[46] Currently, the World Health Organization[47] recommends daily calcium supplementation (1.5-2.0 g oral elemental calcium) for pregnant women with low dietary calcium intake to reduce the risk of preeclampsia, whereas ACOG does not.[1] Medications such as heparin, metformin, sildenafil, and statins, nutritional supplements, and dietary modifications have been or are being explored for the prevention of preeclampsia, but, aside from calcium, none have been identified as efficacious.[48-53]

Acetylsalicylic acid (aspirin) demonstrates inhibitory effects on cyclooxygenases (COX) leading to shifts in the synthesis of prostacyclin and thromboxane A2.[54] This results in a two-fold action, reducing both platelet aggregation and vasoconstriction. Aspirin also leads to reduction in the synthesis of other prostaglandins, such as PGE2, which are involved with inflammation, contributing to aspirin's effect as an anti-inflammatory agent.[55] The inhibition of platelet aggregation and reduced vasoconstriction, as well as aspirin's anti-inflammatory effects[56] are thought to provide the basis by which aspirin administration may reduce the risk of development of gestational hypertension and preeclampsia.[54, 57, 58]

While no interventions eliminate preeclampsia risk, evidence from a moderate-sized body of trial evidence that includes several large trials has established that aspirin modestly reduces the risk of preeclampsia in increased-risk populations.[59-61] Trials conducted among average-risk populations

where preeclampsia prevalence ranges from 3 to 5 percent have not consistently demonstrated preventive benefits, and concerns about potential bleeding from aspirin use as well as lack of data regarding long-term effects on the offspring[56] have supported guidelines focused on increased-risk populations.[1, 62] There have, however, been modeling studies and clinical discussions in recent years arguing for broader use of aspirin for prevention of preeclampsia. Most recently, a large multisite trial conducted in low income and middle income countries reported a statistically significant benefit of low dose aspirin use for prevention of preterm birth and perinatal mortality among nulliparous individuals.[63]

Previous USPSTF Recommendation and Recommendations of Others

In 2014, the USPSTF concluded with moderate certainty that there is a substantial net benefit of daily low dose aspirin use to reduce the risk for preeclampsia, preterm birth, and intrauterine growth restriction in women at high risk for preeclampsia, and 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).

The USPSTF recommendation of low dose aspirin for women at high risk of preeclampsia was evaluated in a retrospective cohort study using a database of deliveries from two hospitals within a single academic institution.[64] Rates of recurrent preeclampsia for women with a history of preeclampsia in a prior pregnancy were compared for periods before and after the 2014 recommendation, spanning recommendation August 2011 to June 2016. Results showed that the risk of recurrent preeclampsia was 30% lower in the "after" group (adjusted relative risk, 0.70; 95% CI, 0.52, 0.95).[64]

Aspirin for women at high risk of preeclampsia is currently the only recommended method of prevention.[1] Low dose aspirin is recommended by the World Health Organization,[65] the American College of Obstetricians and Gynecologists,[66] the National Institute for Health and Clinical Excellence,[67] and the American Heart Association/American Stroke Association (**Table 1**).[68]

Chapter 2. Methods

Scope and Purpose

This systematic review will provide updated evidence regarding the effectiveness of aspirin in reducing adverse maternal, perinatal, and child outcomes, as well as the effectiveness of aspirin in preventing preeclampsia in those at risk. In addition, the harms of aspirin use to prevent preeclampsia will be evaluated. The USPSTF will use this review to update its 2014 recommendation for primary care practices.[69] This review includes all trials from the previous review[70] that met current inclusion/exclusion criteria as well as newly identified studies.

Key Questions and Analytic Framework

We followed USPSTF procedures and methods to define study inclusion and exclusion criteria (**Appendix A Table 1**) and developed an analytic framework (**Figure 1**) with three Key Questions (KQs).

The KQs are:

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

Data Sources and Searches

We considered all studies from the previous review[71] conducted to support the 2014 USPSTF recommendation[72] on this topic for inclusion in the current review and performed a comprehensive search of MEDLINE, PubMed (publisher-supplied only), Embase, and the Cochrane Collaboration Registry of Controlled Trials for relevant studies published between January 2013 and May 15, 2020. This search was designed to partially overlap with the end search dates of the previous USPSTF-commissioned review of this topic, and to identify new studies. Studies included in the previous USPSTF review were evaluated for inclusion against the inclusion and exclusion criteria for the current review. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**).

We also examined the reference lists of other previously published reviews, meta-analyses, and primary studies to identify additional potential studies for inclusion. We supplemented our searches with suggestions from experts and articles identified through news and table-of-contents alerts. We also searched ClinicalTrials.gov (https://ClinicalTrials.gov/) for ongoing trials (**Appendix G**). We imported the literature from these sources directly into EndNote® X9 (Thomson Reuters, New York, NY).

Study Selection

Two reviewers independently reviewed the titles and abstracts of all identified articles to determine whether studies met inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix A Table 1**). Two reviewers then independently evaluated the full-text article(s) of all potentially included studies against the complete inclusion and exclusion criteria. Disagreements regarding the abstract and/or full-text review were resolved by discussion and consultation with a third reviewer if necessary. Excluded studies and reasons for exclusion are listed in **Appendix D**.

We developed an *a priori* set of criteria for inclusion and exclusion of studies with input from USPSTF members and based on our understanding of the literature (**Appendix A Table 1**). For the KQ1 and KQ2 questions of effectiveness, RCTs and individual participant data meta-analyses (IPD-MAs) 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 the KQ3 question evaluating harms, these criteria were expanded to include (1) RCTs conducted in lower or average-risk populations; and (2) 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. **Appendix A Table 1 lists all** outcomes that were considered for inclusion in the review. Studies limited to persons seeking fertility treatments were not included. Only studies of daily aspirin (≥ 50 mg) for the primary prevention of preeclampsia were considered for inclusion, but studies evaluating nonaspirin antiplatelet medications or aspirin combined with other potentially active interventions (e.g., dietary supplements, weight loss), or studies of aspirin aimed at preventing other complications of pregnancy such as miscarriage, were not. 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.[73] We also limited our included studies to those published in English and deemed good- or fair-quality based on USPSTF quality rating standards.[74]

Quality Assessment and Data Abstraction

Two reviewers applied USPSTF design-specific criteria to assess the methodological quality of all eligible studies (**Appendix A Table 2**). We assigned each study a quality rating of "good," "fair," or "poor." Discordant quality ratings were resolved by discussion or 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 of the specified quality criteria (e.g., comparable groups were assembled initially and maintained throughout the study, followup was 90% or higher, assessment procedures were described and blinded if they involved direct interviews, randomization methods were described, allocation was concealed). 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 generally had several important limitations, including at least one of the following risks of bias: very high attrition (generally > 40%); differential attrition between intervention arms (generally > 20%); lack of baseline comparability between groups without adjustment; or problematic issues in trial conduct, analysis, or reporting of results (e.g., possible selective reporting; inappropriate exclusion of participants from analyses; questionable validity of allocation or assessment procedures).

For all of the included studies, one reviewer extracted key elements into standardized abstraction forms in DistillerSR (Evidence Partners, Ottawa, Canada). Key elements included general characteristics of the study (e.g., author, year, study design), clinical and demographic characteristics of the sample and setting (e.g., age, race/ethnicity, baseline clinical characteristics, setting, country), analytic methods, and results. A second reviewer checked the data for accuracy.

When abstracting reported data on health outcomes, we included the number of participants experiencing an event, as well as incidence rates, as appropriate. For KQ1, we abstracted the following maternal health outcomes: eclampsia, puerperal cerebrovascular disorder, cerebrovascular hemorrhage, edema, or embolus; renal or hepatic injury/failure; pulmonary edema; mortality; mental health diagnoses or symptoms; and any reported measures of well-being. Fetal, neonatal, and child health outcomes included preterm delivery; mean gestational age; low birth weight; intrauterine growth restriction/small for gestational age; and stillbirth or neonatal mortality. The study defined definitions of outcomes were described and the most commonly reported were combined for meta-analysis. Where available, we aimed to abstract information on the number of early and very early preterm births, and separate cases of spontaneous from induced preterm birth. For KQ2 (preeclampsia prevention effectiveness), we abstracted the incidence of preeclampsia reported in each RCT. For KQ 3 (harms of aspirin use for preeclampsia prevention), we abstracted reports of abruptio placentae, intracranial fetal bleeding, postpartum hemorrhage or estimated blood loss, and any other major harm to the mother or fetus reported.

Data Synthesis and Analysis

This review was conducted in accordance with current USPSTF procedures and systematic review methods.[74] Tables describing key study design and participant characteristics were created. Pooled effect estimates of the relative risks of health outcomes associated with aspirin use were generated using random effects model with restricted maximum likelihood (REML) and Knapp-Hartung adjustment methods.[75, 76] This analytic approach overcomes limitations of other estimators for tau-square that have been found to generate overly precise confidence limits, especially when pooling fewer than 20 studies.[77] For rare outcomes (i.e., perinatal mortality) we

conducted sensitivity analyses using the Peto odds ratio method,[78] as well as pooled analyses including and excluding studies that had no events in either study arm, to assess the robustness of the final RR pooled estimates.[79] We identified study design and participant characteristics that could possibly explain heterogeneity in aspirin effectiveness among the included studies. To examine subgroup differences, we generated stratified forest plots using the Cochran Q statistical test for interaction and conducted REML meta-regression analyses using the Knapp Hartung correction. Variables anticipated *a priori* to be potential sources of heterogeneity included aspirin dosage, timing, and duration; population risk characteristics (e.g., incidence of preeclampsia in the control condition, strategy for selecting participants); study size; and control condition (i.e., placebo versus no treatment). We defined comparison groups based on clinically meaningful distinctions. For comparisons of effects by population risk of preeclampsia, we compared studies where more than 12 percent of participants developed preeclampsia in the control group to studies with lower incidence rates. This threshold was selected to distinguish trials with approximately 3 times incidence seen in the general population. We also compared studies that used a Doppler ultrasound test as part of the risk assessment procedure with those that did not, and studies that used any lab or imaging tests compared to those relying only on clinical history and exams. For each KQ, the statistical heterogeneity of included studies was estimated with I^2 statistics and Tau^2. The distribution of trial results was examined with funnel plots and Peters tests to assess whether there was evidence of small-study effects.[80-82]

In accordance with published methodological guidance on evaluating subgroup effects within trials,[83] we abstracted the results of within study differences to support inferences related to subgroup effects only if statistically valid tests for interaction were reported.

For each outcome measure, we calculated the number needed to treat (NNT) by first estimating the absolute risk reduction based on the pooled risk ratio and two to three estimated levels of baseline risk of the outcome of interest (i.e., absolute risk reduction=(risk ratio-1)*population risk). Because there was a wide range of risks for some of the outcomes (preeclampsia, SGA/IUGR, preterm birth), we selected population risk levels empirically using the included studies corresponding to the 20th, 50th, and 80th percentiles of outcome incidence in the control arm of the trials. For perinatal mortality we used the lowest and highest incidence levels reported in trials included in the pooled analysis for this outcome. From the absolute risk reduction for every level of baseline risk tested, we calculated the NNT as the inverse of the absolute risk ratio.[84]

We used Stata version 16.1 (StataCorp LP, College Station, TX) for all analyses. All significance testing was two-sided, and results were considered statistically significant if the p-value was 0.05 or less.

Grading the Strength of the Body of Evidence

The strength of the overall body of evidence for each KQ was graded using an adaptation of the Evidence-based Practice Center approach,[85] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[86] This adaptation explicitly addresses four of the five Evidence-based Practice Center-

required domains: 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 (i.e., study limitations, risk of bias). We do not evaluate the fifth domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there was insufficient evidence for a particular outcome). Study quality summarizes the quality ratings of the individual trials included for an outcome and indicates the degree to which the results are likely to have adequately low risk of bias. The limitations domain highlighted important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients).

The overall strength of evidence was graded as "high," "moderate," "low," or "insufficient." "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. At least two independent reviewers rated the overall strength of evidence for each intervention type. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft Research Plan for this review was posted for public comment on the USPSTF website from June 20 to July 23, 2019. Several minor additions and wording changes were made to improve the clarity and specificity of the inclusion criteria. Additional clinically important categories used for defining preeclampsia and preterm birth were included to more fully represent health outcomes that may be reported in the literature. A final research plan was posted on the USPSTF website on September 26, 2019.

A draft version of this report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report when appropriate. Additionally, a draft of the report was posted for public comment on the USPSTF Web site from February 23, 2021 through March 23, 2021. The draft received very few comments, leading to small editorial changes but no updates to the included evidence or our conclusions.

USPSTF Involvement

We worked with four USPSTF members at key points throughout this review, particularly when determining the scope and methods for the review and when developing the Analytic Framework and Key Questions. After revisions reflecting the public comment period, the USPSTF members approved the final analytic framework, KQs, and inclusion and exclusion criteria. AHRQ funded this review under a contract to support the work of the USPSTF. An AHRQ Medical Officer provided project oversight, reviewed the draft report, and assisted in the external review of the report.

Chapter 3. Results

Description of Included Studies

Our literature search yielded 3749 unique citations. From these, we reviewed the full text of 183 articles (**Appendix B Figure 1**). Of these, 23 studies (33 articles) met our inclusion criteria. We excluded the remaining 150 full-text articles (**Appendix C**).

Of the 23 included studies (n=26,952) 19 are carried forward from the previous USPSTF review conducted in 2014.[57, 87-104] These studies met the inclusion and exclusion criteria of the current review and were combined with four newly identified RCTs.[59, 105-107] Four studies included in the previous review were excluded based on risk of bias and eligibility determinations according to the scope of the current review.[108-111] Among the included studies, 18 (10 good-quality) met the inclusion criteria for KQ 1 (maternal and perinatal health outcomes); 16 (10 good-quality) met the inclusion criteria for KQ 2 (preeclampsia); and 21 (14 good-quality) met the inclusion criteria for KQ 3 (harms). One IPD-MA was identified but was not included because our prespecified inclusion and exclusion criteria for intervention and setting were not met. The results of this study are discussed in the next chapter. For KQs 1 and 2, we included trials that enrolled pregnant individuals at increased risk of preeclampsia. For KQ 3 we included studies reporting harms from trials enrolling pregnant individuals at increased risk (16 included trials) and at average risk of preeclampsia (5 included trials) (**Appendix B Figure 1**).

Population and Setting Details

Tables 2 and 3 provide summary information on study population, setting, design, and intervention characteristics of the included studies. For KQ 1 and KQ 2, assessing the effectiveness of aspirin in preventing preeclampsia and related health outcomes for pregnant individuals at increased risk for preeclampsia, we included a large Maternal Fetal Medicine Unit Network in High Risk Women (MFMU-HR) trial (n=2,539) funded by National Institute of Child Health and Human Development that recruited participants from 13 clinical sites in the United States from May 1991 to June 1995.[99] Two large international trials coordinated from the United Kingdom were also included:[59, 95] The Collaborative Low dose Aspirin Study in Pregnancy (CLASP) (n=9,364) trial enrolled participants from 213 centers across 16 countries from January 1988 to December 1992,[95] and the Combined Multimarker Screening and Randomized Treatment with Aspirin for Evidence-based Preeclampsia Prevention (ASPRE) trial (n=1,776) enrolled participants 13 maternity hospitals based in 6 countries (United Kingdom, Spain, Italy, Belgium, Greece, Israel) from April 2014 to April 2016.[59] There were 15 smaller trials included from various countries.[57, 87-90, 93, 94, 96-98, 101, 103, 104, 106, 107] For KQ 3, assessing harms associated with aspirin use during pregnancy, we included five additional RCTs of women considered to be at average risk for preeclampsia.[91, 92, 100, 102, 105] These five RCTs included a good-quality multisite study conducted in the United States MFMU sites that enrolled average- or low-risk participants (MFMU-LR) (n=3,135),[92] a smaller U.S.-based study (n=606),[91] a large good-quality multisite study in France and Belgium (n=3,294),[102] a large good-quality hospital-based study in Barbados (n=3,647),[100] and a smaller fair-quality study from Ireland (n=362).[105]

Among trials included to assess the effectiveness of aspirin, a variety of study procedures and criteria were used to identify populations of pregnant persons at increased risk for preeclampsia (**Table 4**). The most common method was examination of participant characteristics and personal or family medical history (e.g., age, BMI, parity, multifetal gestation, history of hypertensive disorders, history of pregnancy complications). Among these studies, history of hypertensive disorders (preeclampsia, gestational hypertension, or chronic hypertension), alone or in combination with other risk factors, was used as the primary method to identify trial participants in ten studies,[57, 88, 89, 93, 95, 97-99, 101, 104] and multifetal gestation was used in six trials.[57, 89, 94, 95, 98, 99] Other clinical risk factors used included metabolic disease;[57, 98] diabetes (prepregnancy or gestational),[99, 104] history of IUGR/SGA,[88, 101, 104] spontaneous abortion,[57, 98, 104] or stillbirth;[88, 101] renal disease;[95, 97] and maternal age.[57, 95, 98]

Most risk factors and clinical tests used for identifying increased-risk populations, whether used alone or in combination with other factors, were associated with at least a two-fold higher risk for preeclampsia. An exception to this was nulliparity, which is understood to be a more modest independent risk factor for preeclampsia. Nulliparity was combined with other risk factors to identify an increased-risk population in three of the effectiveness trials.[57, 89, 98, 107] Nulliparity alone was used to select participants in four of the five studies enrolling average-risk populations that were included for evaluating harms of aspirin use in pregnancy.[91, 92, 102, 105] These studies, which reported preeclampsia incidence in the control condition ranging from 2 to 6 percent (similar to the population average), were not included for evaluating KQ1 and KQ2 as nulliparity alone was not considered sufficient evidence of increased risk in accordance with the scope defined for the previous and current review.

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 six studies.[59, 90, 103, 104, 106, 107] One study relied on angiotensin-II sensitivity identified via blood pressure response to IV infusion of angiotensin II.[87] Another required a positive rollover test in which rolling the participant from her left side to her back resulted in rise of diastolic blood pressure >15 mg Hg above baseline.[89] One study used a second trimester hemoglobin concentration greater than 13.2 g/dL to determine the risk of an individual participant in the trial.[96] Finally, one trial utilized a prediction model that combined maternal demographic factors and medical history, mean arterial pressure, uterine-artery pulsality index, and maternal serum pregnancy-associated plasma protein A and placental growth factor to identify persons at increased risk for preterm birth secondary to preeclampsia.[59]

The inclusion and exclusion criteria in the trials were usually well described, but details on the baseline demographic characteristics and risk factors of enrolled participants were sparsely and inconsistently reported (**Appendix E Table 1**). Overall, the population of women included in the trials was young (mean age ranging from 20.4 to 33.5 years) and predominantly White, with only three trials reporting majority populations of Black women (ranging from approximately 50% to 72%).[91, 92, 99] Parity was reported in most trials, with the proportion nulliparous ranging from approximately 15 to 100 percent of study participants. Similarly, the proportion of participants with a history of chronic hypertension at baseline ranged from no participants (in low or average-risk population studies included for KQ3) to nearly all having this history (91%). History of

smoking and current smoking were reported in 13 trials and ranged from approximately 10 to 40 percent of participants.[59, 87, 88, 90, 92, 95, 96, 99, 102-106] Mean BMI ranged from 22.3 to 29.7 kg/m^2 in the studies reporting this baseline characteristic.

Intervention Characteristics

Included trials varied widely in timing of and dosages of aspirin treatment (**Table 2, Table 3**). The gestational age at which aspirin therapy was initiated across the trials varied substantially with nine trials starting therapy in participants as early 11 to 12 weeks of gestation and five allowing initiation to continue as late as 36 to 38 weeks of gestation. The most common date of aspirin discontinuation was delivery, but eight trials stopped aspirin prophylaxis before delivery,[59, 89, 97, 101-105] as early as 34 weeks[102] or at the point when preeclampsia developed.[99] Aspirin dosages ranged from 50 to 150 mg daily. The majority of trials used either dosages of 60 mg (6 trials)[87, 88, 91, 92, 95, 99] or 100 mg (9 trials);[57, 89, 94, 97, 98, 101, 102, 104, 107] two of the newly identified trials used a higher dose of 150 mg per day.[59, 106] A matching placebo was the comparator in all trials except in one study included for harms, in which participants in the control arm received usual care with no placebo.[105]

Meta-analysis was possible for seven outcomes that were reported with enough consistency across multiple studies to support valid estimation of effects. The relevant results related to each Key Question are presented in detail below (**Table 5**). The three largest included trials, MFMU-HR, CLASP, and ASPRE,[59, 95, 99, 112-117] conducted prespecified or exploratory comparisons and reported statistical tests for interaction suitable for evaluating subgroup differences (**Appendix F, Table 1**).

KQ1. Does Aspirin Reduce Adverse Maternal, Perinatal, Child, or Combined Health Outcomes in Pregnant Persons at Increased Risk of Preeclampsia?

Summary of Results

Eighteen trials (n=15,908) reported maternal, perinatal, or child health outcomes for daily aspirin use (50mg to 150mg daily) 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 5)**. Preventive effects of aspirin on the three main outcomes ranged from 20 to 30 percent reduced risk. Evidence from one within-trial comparison indicated that aspirin may be more effective among nonsmokers than among smokers. Aggregate comparisons between different design and participant characteristics of the included studies suggested that the benefit of aspirin for preventing preterm birth may be larger when aspirin was started before 16 weeks of gestation than when started later. There also was evidence of a larger effect of aspirin for preventing preterm birth in studies enrolling a larger proportion of nulliparous participants (who also had other risk factors). We did not observe statistically significant differences between specific populations for the preeclampsia or SGA/IUGR outcomes, and differences for preterm

birth could be attributed to multiple comparisons. Nevertheless, small-study effects could not be ruled out and might lead to some overestimation of pooled effect sizes. Confounding of study size with other study and participant characteristics could have influenced subgroup comparisons. For example, the two largest studies reported the smallest risk reductions for all outcomes, but these studies also both started treatment later than 16 weeks of gestation and used very low aspirin dosages. Other rare health outcomes, such as eclampsia and maternal mortality, occurred too infrequently to estimate preventive effectiveness.

Detailed Results

Maternal Health

Direct maternal health consequences of preeclampsia are extremely rare and include eclampsia, HELLP syndrome, stroke, organ failure, and death. Few trials reported these events, 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 (**Appendix E Table 2**). Many of the perinatal outcomes described below also have implications for maternal health and well-being, as do outcomes described as potential harms for KQ3.

Perinatal Mortality

Fifteen trials reported on perinatal mortality (N =15,527). Four of these reported no perinatal deaths in either study arm and were not included in the pooled analysis.[89, 96, 98, 107] Seven reported two or fewer events in one or both study arms.[57, 87, 88, 90, 93, 94, 97] No individual study reported a statistically significant difference in perinatal mortality and all were underpowered for this outcome, but the pooled effect estimate showed a statistically significant 21 percent reduction in the risk of perinatal mortality associated with aspirin use (pooled RR 0.79, 95% CI 0.66, 0.96; I^2 0%; k=11, n=13,860) (**Figure 2, Appendix E Table 3**). The pooled effect was consistent with the findings from the three largest trials, which reported more cases of perinatal mortality in the control group than in the aspirin group, with relative risks ranging from 0.59 to 0.80. Smaller trials reported effects that were less consistently in the direction of a benefit, but confidence intervals were overlapping.

Preterm Birth

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 estimated pooled effect showed a 20 percent reduced risk of preterm birth associated with intervention (pooled RR 0.80, 95%CI 0.67, 0.95; I^2 49%; k=13, n=13,619) (**Figure 3, Appendix E Table 4**). The primary outcome of the ASPRE trial[59] was "preterm preeclampsia" a composite of preeclampsia and preterm birth. For pooled analyses, we used reported data from this trial to compute a preterm birth outcome consistent with what was reported in all other trials: preterm birth with or without a preeclampsia diagnosis. The combination of preeclampsia and preterm birth is a less common outcome, with ASPRE reporting 1.6 percent (13/798) in the aspirin group and 4.3 percent (35/822) in the placebo group, and the reported effectiveness of aspirin for the

outcome (OR 0.38, 95%CI, 0.20, 0.74) was greater than for the prevention of any preterm birth. Nevertheless, the computed relative risk of any preterm birth for the ASPRE trial also favored aspirin (RR 0.65, 95% CI, 0.47, 0.90). Trials rarely reported cases of spontaneous preterm birth separately from induced preterm birth, and few studies reported the number of cases of very early and early preterm birth included in the preterm birth outcome.

Small for Gestational Age or Intrauterine Growth Restriction

Sixteen trials reported on SGA/IUGR (N = 15,757) and all but two[90, 99] reported fewer cases in the aspirin group than in the placebo group. The estimated pooled effect indicated a 18 percent reduced risk of having an SGA/IUGR infant for women who took aspirin (pooled RR 0.82, 95% CI 0.68, 0.99; I^2 41%; k=16; n=14,385) (**Figure 4, Appendix E Table 5**).

Studies did not consistently report birthweight or gestational age at birth, but the results that were reported are consistent with the aspirin effects on SGA/IUGR and preterm birth (**Appendix E Tables 6 and 7, Appendix F Figure 1**). Combined mean birthweight (grams) was higher with aspirin use than with placebo across eleven studies (n=10,987) that reported the outcome (weighted mean difference 126.9; [95%CI 39.8, 214.0]; I^2 50.0%).

Small-Study Effects

Tests for small-study effects were statistically significant for preterm birth (Peters p = 0.026) and approached statistical significance for SGA/IUGR (Peters p = 0.072) (data not shown). This suggests that the pooled effects for these outcomes may overestimate the effectiveness of aspirin due to differences in the way smaller studies were conducted or the absence of small null or negative studies in the published literature. Visual inspection of funnel plots also revealed an imbalance of the distribution of study findings and standard errors consistent with the statistically significant test for small-study effects. Because random effects meta-analysis modeling weights smaller studies more heavily, they can exacerbate bias due to small-study effects.[84] The fixed effect sensitivity analysis (data not shown) suggests that the random effect estimates for SGA/IUGR and preterm birth could be slightly overestimated due to small-study effects, but that the random effects confidence intervals provide good coverage for the range of likely effects.

KQ1a. Does the Effectiveness of Aspirin for Reducing Adverse Health Outcomes Vary by Subpopulations Defined by Personal Characteristics or Preeclampsia Risk Factors?

Valid tests for subgroup differences were available from the three largest trials (**Appendix F Table 1**).[95, 99, 112] We conducted subgroup comparisons at the aggregate level using stratified forest plots and meta-regression. Subgroup differences were assessed for the outcomes of preterm birth (<37 weeks of gestation) and SGA/IUGR since these outcomes had enough studies and precision to reasonably support statistical comparisons between groups (**Appendix F Figure 3 and Figure 4**). These study level comparisons should be interpreted with reservations given

the evidence of small-study effects for these outcomes and others, and as the two largest trials started aspirin use later in pregnancy (≥16 weeks of gestation) and used very low aspirin dosages (60mg).

Aspirin Timing and Dosage

The CLASP trial compared the effect of aspirin (60 mg) initiated at ≤20 weeks versus >20 weeks of gestation for preventing preterm birth, SGA/IUGR, and perinatal mortality and found no statistically significant differences (**Appendix F Table 1**).[95] Similarly, no differences were found in the MFMU-HR trial for comparisons of participants initiating aspirin before or after 16 weeks of gestation.[99]

In across study comparisons of subgroup study effects, a comparison of the pooled relative risk of IUGR/SGA between studies with aspirin started before 16 weeks of gestation (pooled RR, 0.59 [95% CI, 0.41, 0.86], I^2 35%, k=6, n=2,351) and those where the majority of participants began daily aspirin use later (pooled RR, 0.95 [95% CI, 0.80, 1.13], I^2 16%, k=10, n=12,034) was statistically significant (p=0.03) **(Figure 5, Appendix F Figure 3)**. For prevention of preterm birth, there was further evidence that aspirin is more effective if started before 16 weeks of gestation, but only four studies reporting the outcome were in the earlier initiation subgroup; there was a statistically significant difference between the pooled relative risk of preterm birth associated with initiation of aspirin before 16 weeks of gestation (pooled RR, 0.49 [95% CI, 0.26, 0.95], I^2 28%, k=4, n=2,103) and the estimate from studies where the majority of participants began aspirin later (pooled RR, 0.91 [95% CI, 0.85, 0.96], I^2 0%, k=9, n=11,516) (p=0.02) **(Figure 6, Appendix F Figure 4)**.

There was not a statistically significant difference in effectiveness related to the dosage of aspirin used in trials for the SGA/IUGR outcome (**Appendix F Figure 3**), but for preterm birth, greater risk reductions were seen in trials with dosages greater than 75mg/d (pooled RR, 0.68 [95% CI, 0.52, 0.88], I^2 22%, k = 9, n = 3,065) compared to those using lower doses (pooled RR, 0.91 [95% CI .81, 1.02], I^2 0%, k = 4, n = 10,554) (**Appendix F Figure 4**).

Very few studies with large n's contributed to the estimation of the effect for doses <75 mg/d, however, and it is not possible to determine whether shared study design and population characteristics, account for the association.

Personal Characteristics and Clinical History

The CLASP trial found no significant difference in the effectiveness of aspirin or preventing perinatal mortality, IUGR, and preterm birth (<37 weeks of gestation) between multiparous and nulliparous study participants. The MFMU-HR trial compared preterm birth and SGA outcomes by BMI and smoking status. Only one of these contrasts was statistically significant—the effectiveness of aspirin (60 mg/day) to prevent preterm birth among nonsmokers (RR 0.91, 95%CI 0.84, 0.99) was greater than for smokers (RR 1.17, 95% CI 0.99, 1.39) (p=0.01) (**Appendix F Table 1**). The ASPRE trial tested differences in aspirin effectiveness for preventing preeclampsia with preterm birth for several personal characteristic and clinical history

factors including maternal age, BMI, racial origin (Afro Caribbean, Caucasian, Other), assisted versus natural conception, smoking status, family history of preeclampsia, parity, and diagnosed chronic hypertension, but did not identify any statistically significant differences. Several of these post-hoc comparisons were limited by relatively small numbers of participants in specific subgroups, and low event rates for this primary outcome resulted in wide confidence intervals.

In study level comparisons, there was a significantly stronger effect of aspirin on prevention of preterm birth in studies in which a majority (more than 50%) of participants were nulliparous than in those in which nulliparous participants were a minority (**Appendix F Figure 4**). Again, however, few studies were available for comparisons, limiting interpretation of the association.

Preeclampsia Risk Assessment Approach

Differences among trials in their criteria for identifying populations at increased preeclampsia risk were not associated with differences in the effectiveness of aspirin for prevention of preterm birth or SGA/IUGR. Trials that used risk assessments based on clinical history rather than clinical tests or prediction models were not found to be less effective at identifying a population that benefited from aspirin (**Appendix F Figure 3 and Figure 4)**. There was also no significant difference between effects of aspirin use on prevention of SGA/IUGR or preterm birth in studies that used abnormal Doppler ultrasound as part of the risk assessment with those that did not. There were also no significant differences in the estimated effectiveness of aspirin in studies where more or less than 12 percent of participants in the placebo group developed preeclampsia, although absolute risk reductions were greater when the incidence of preeclampsia in the control group was higher.

KQ2. Does Aspirin Prevent Preeclampsia in Pregnant Persons at Increased Risk for Preeclampsia?

Summary of Results

Aspirin use was started as early as 11 weeks of gestation and as late as 32 weeks of gestation at dosages of 50 to 150mg per day in the 16 RCTs (N=15,767) reporting preeclampsia outcomes for pregnant individuals at increased risk. The meta-analysis estimated a statistically significant 15 percent reduced risk of preeclampsia for aspirin treatment relative to placebo. The possibility that this risk reduction is overestimated could not be ruled out. We found evidence of small-study effects that could be due to the absence of smaller studies with null or negative findings in the published literature or differences in the ways smaller studies were conducted (e.g., aspirin protocols, populations enrolled, implementation, study quality). The two largest trials found modest, nonsignificant within study effects of 10 to 12 percent reduced risk of preeclampsia, however, these trials also used lower doses of aspirin than many of the other trials. Across the trials, approaches for identifying individuals at increased risk varied, as did the inclusion and exclusion criteria, generating a broad range of absolute risk reductions. We found no evidence of statistically significant differences in the magnitude of preeclampsia risk reductions related to the timing of treatment initiation; the dosage of aspirin used; or personal characteristics such as

smoking history, parity, and BMI, nor were the approaches to assessing preeclampsia risk or the incidence of preeclampsia observed in the study population related to differences in effectiveness.

Detailed Results

Sixteen included RCTs (N = 15,767) reported on the effectiveness of aspirin to prevent preeclampsia (**Table 5, Appendix E Table 8**). Across these studies, the incidence of preeclampsia in the placebo condition ranged from 4 to 30 percent, reflecting the broad range of criteria used for identifying increased-risk populations (**Table 4**). Aspirin was associated with a statistically significant reduction in the risk of preeclampsia compared to placebo (pooled RR, 0.85 [95% CI, 0.75 to 0.95], I^2 0%, n = 14,093) (**Figure 7**). Effects were consistent across the included studies; all but two small studies reported effects in the direction of a treatment benefit.[101, 106] Of the largest trials, two using 60mg aspirin reported approximately 10 percent risk reductions with confidence intervals that were not statistically significant [95, 99] and a more recent large trial using 150mg aspirin showed a statistically significant 28 percent reduction in the risk of preeclampsia.[59]

A test for small-study effects was statistically significant (Peters p = 0.035), suggesting that the pooled effect may overestimate the effectiveness of aspirin for this outcome due to publication bias or differences in the ways smaller studies were conducted. Visual inspection of a funnel plot also showed a tendency for larger studies to report smaller effect sizes. Because random effects meta-analysis models weight smaller studies more heavily, they can exacerbate bias due to small-study effects. Therefore, we conducted sensitivity analyses for the preeclampsia outcome using fixed effects meta-analysis. Unlike the findings for health outcomes, the fixed effects result for preeclampsia was less conservative, estimating 17 percent risk reduction with greater precision than the random effects model. Thus, we did not find evidence that the random effects modeling approach resulted in overestimation of the effect for this outcome, possibly due to the lack of statistical heterogeneity seen for the outcome.

Other Hypertensive Disorders of Pregnancy

Half of the studies reporting preeclampsia also reported the effectiveness of aspirin for prevention of gestational hypertension (k=9, N=2,789). Meta-analysis of this outcome showed inconsistency of effects, imprecision, and higher statistical heterogeneity than for more commonly reported outcomes, and could not include the two largest trials; it did not find a significant effect of aspirin use on gestational hypertension (pooled RR 0.74, [95%CI, 0.46, 1.18], I^2 51%, k=9, n=2,591) (**Appendix E Table 9, Appendix F Figure 2**). An analysis of 8 studies where it was possible to combine cases of gestational hypertension with cases of preeclampsia to create a composite outcome measure of hypertensive disorders of pregnancy showed a statistically significant effect of aspirin use (RR 0.65; [95%CI 0.44, 0.96]; I^2 59.4%) (data not shown), but the result cannot support strong inferences given the exclusion of the two largest trials from the analysis and substantial clinical and statistical heterogeneity.

KQ2a. Does the Effectiveness of Aspirin for Reducing Preeclampsia Vary by Subpopulations Defined by Personal Characteristics or Preeclampsia Risk Factors?

Valid tests for subgroup differences were available from the two largest trials.[95, 99] We also conducted subgroup comparisons at the aggregate level using stratified plots and meta-regression.

Aspirin Timing and Dosage

Both of the largest trials (CLASP and MFMU-HR) reported tests for differences in aspirin effectiveness according to the timing of initiation; however, none of the comparisons were statistically significant (the CLASP trial required a 99% confidence range for tests of subgroup effects to account for multiple comparisons) **(Appendix F Table 1**).

In aggregate, in subgroup comparisons with the included studies in this review, we did not find an effect of aspirin administration timing on preeclampsia risk. The pooled risk reduction in studies initiating aspirin before 16 weeks of gestation was lower (RR, 0.68 [95%CI, 0.53 to 0.89], I^2 0%, k=5, n=2,346) than for studies with later initiation (RR, 0.88 [95% CI, 0.77 to 1.00], I^2 0%, k=11, n=11,747) but the difference was not statistically significant (p=0.08) (**Figure 8**).

There was also not a statistically significant difference in aspirin effectiveness by dosage in aggregate stratified analyses. Preeclampsia risk reduction with ≥75 mg of aspirin (RR, 0.72 [95% CI, 0.56, 0.93]) was slightly greater compared with <75 mg (RR, 0.89 [95% CI, 0.74, 1.07]), but the test for an interaction was not statistically significant (p=0.10) (**Appendix F Figure 5**). Analyses comparing dosages at or above 100mg to lower dosages also did not yield statistically significant interactions. We also did not find any indication of a dose-response relationship in forest plots sorted by aspirin dosage.

Personal Characteristics and Clinical History

The CLASP trial found no evidence of differences in effectiveness of aspirin use (60mg) for reducing preeclampsia between nulliparous versus multiparous study participants. Comparisons from the MFMU-HR trial found no evidence of differences in the effectiveness of aspirin for preeclampsia according to BMI (<30 versus ≥30 kg/m^2) or reported smoking during pregnancy (**Appendix F Table 1**). **S**tratified estimates of the effectiveness of aspirin by broad racial categories were conducted in the MFMU-HR trial, but statistical tests for interaction were not conducted; a smaller magnitude risk reduction was reported for "nonWhite" participants but the confidence intervals overlapped for the two strata (data not shown).

Meta-regression comparisons of subgroups of the included studies for this outcome did show a significant difference in aspirin effectiveness associated with the proportion of participants who were nulliparous. The effect size was estimated to be somewhat greater in the studies where

more than half of participants were nullipara at increased preeclampsia risk (RR, 0.64 [95% CI, 0.46, 0.89]) compared to those with fewer nullipara (RR, 0.89 [95% CI, 0.80, 0.99]) (p=0.02). (**Appendix F Figure 5**). Differences in other characteristics of these studies could account for this trend, but there were too few studies included in the review to adjust for potential confounders by including additional covariates in meta-regression.

Preeclampsia Risk Assessment Approach

We did not observe significant differences in the estimated effectiveness of aspirin for prevention of preeclampsia based on how studies identified an increased-risk population, nor between studies that identified populations where more or less than 12 percent of participants developed preeclampsia (**Appendix F Figure 5)**.

KQ3. What Are the Harms of Aspirin Use to Prevent Preeclampsia During Pregnancy?

Summary of Results

Data from 21 trials (N= 26,757) provided evidence on potential harms of daily low dosages of aspirin. 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. We did not identify greater risks of placental abruption, postpartum hemorrhage, or fetal intracranial bleeding in participants treated with aspirin than those who were not in pooled analyses, nor were there differences within studies for less commonly reported and more rare perinatal harms. There was no evidence to indicate differences in these risks by the dosage or timing of aspirin used in the studies. Longer-term followup from one large multicenter trial was also reassuring, finding no difference in child developmental harms associated with aspirin for preeclampsia prevention taken during pregnancy. Finally, there were no significant differences found between treatment and control groups for other reported side effects or complications such as NICU admissions, rates of Cesarean deliveries, petechiae, purpura, and other instances of singular adverse events; and aspirin was generally well tolerated.

Detailed Results

We analyzed data from 21 trials on potential harms of aspirin use throughout pregnancy for the prevention of preeclampsia. Sixteen of the included trials reporting harms outcomes were conducted among pregnant individuals at increased preeclampsia risk and five were among average-risk populations. Daily aspirin doses ranged from 50mg to 150mg per day and start times ranged from 11 to 32 weeks of gestation. Pooled analyses were possible for three reported outcomes related to potential bleeding harms of aspirin use (**Table 5**).

Postpartum Hemorrhage

There was not a statistically significant difference in the risk of postpartum hemorrhage (most commonly defined as ≥ 500 mL blood loss) in 11 trials (N=23,583) randomized to aspirin or placebo (pooled RR 1.03, [95% CI, 0.94, 1.12] I^2 0%, k=9, n=23,133). Most large trials consistently reported postpartum hemorrhage as a trial outcome, with the exception of the recent ASPRE trial. There was not a statistically significant difference in the risk of postpartum hemorrhage for average-risk versus increased-risk study populations (p = 0.12) (**Figure 10, Table 5, Appendix E Table 10**).

Placental Abruption

Thirteen trials (N=25,761), seven conducted among increased-risk populations and five in average-risk populations, reported placental abruption. Three of the trials reported no cases in either study arm,[93, 94, 98] and three additional trials reported 2 or fewer cases in one or both study arms.[91, 96, 105] There was not a statistically significant difference between groups in the risk of abruption in meta-analysis (pooled RR, 1.15 [95% CI, 0.76, 1.72] I^2 25%, k=10, n=24,970) and this effect did not differ between studies of average-risk and increased-risk populations (p = 0.41) (**Figure 9, Table 5, Appendix E Table 11**).

Infant Bleeding Outcomes

Aspirin was not associated with a difference in the risk of fetal intracranial bleeding (cerebral or intraventricular hemorrhage) in a meta-analysis of nine trials (N=23,959) using daily doses ranging from 60mg to 150mg (pooled RR, 0.90 [95% CI, 0.51, 1.57]; I^2 19%, k=6, n=23,719) (**Figure 11, Table 5**). The outcome is rare—three trials reported one or fewer cases (**Appendix E Table 12**). Two trials reported cases of cephalohematoma; one small trial reported a single case in the control group[89] and a larger trial reported more cases in the intervention condition (68/1480, 4.6%) compared to placebo (55/1505, 3.7%); however, the relative risk in the larger trial was imprecise because of the low event rate (RR, 1.26, [95% CI, 0.89, 1.78]).[92] The same trial reported a composite outcome defined as any infant bleeding disorder, again finding slightly more cases in the aspirin group than the placebo group (7.0% vs. 6.5%) but not a statistically significant difference (RR, 1.08, [95% CI, 0.83, 1.41]).

Congenital Malformations and Other Infant Outcomes

Four trials reported on congenital anomalies or malformations (N= 2,283), which were very rare (**Appendix E Table 12**). Three of the trials reported more cases in the placebo group[59, 97, 105] and one small trial reported a single case of anencephaly that occurred in the aspirin group.[93] One trial reported cases of respiratory distress syndrome, with more occurring in the placebo group, but there was statistical imprecision in the estimated odds based on the study reported confidence interval estimated for this secondary outcome (aOR 0.53, [99% CI, 0.20, 1.40]).

Longer-Term Infant Harms

The CLASP trial conducted followup surveys and reported on longer-term child health outcomes for participants from trial sites in the United Kingdom and Canada. This included developmental outcomes at age 12 months (n=4,168 – United Kingdom followup data) and 18 months (n=4,365 – United Kingdom and Ottawa followup data). The trial found no differences in hospital visits, gross motor development, or height and weight measurements between treatment groups (**Appendix E Table 13**).

Other Maternal and Infant Complications

In addition to the primary, more commonly reported potential harms of aspirin evaluated above, some trials also reported on other adverse events (**Appendix E Table 12**). For the most part, comparisons between study groups for these outcomes provide assurance of the safety of aspirin during pregnancy. A large trial conducted with an average-risk population using a 75mg/day aspirin dose (n=3647) reported no differences in duration of hospital stay, prenatal hospital admission, blood transfusions, or rates of induced labor between participants taking aspirin than those taking placebo.[100] Another large trial in an average-risk population using a 60mg/day dose (n=2985) reported similar results, with no significant differences in newborn rates of petechiae, purpura, excessive bleeding with circumcision, or any bleeding disorders between the two study groups.[92] Further, there were no significant differences in the need for transfusions between those taking aspirin and those taking placebo, and no cases of bleeding complications among women who received aspirin and epidural anesthesia. The MFMU-HR trial (n=2503) reported no differences in a composite measure of any adverse events for mothers or neonates, but provided few details.[99] In the CLASP trial there were fewer cases of infants admitted to special care units in the treatment group, and the duration of stay was similar between treated and untreated infants. In the aspirin-treated group, however, significantly more women needed a blood transfusion after delivery (4.0% vs. 3.2%, significance test not reported). The higher rate of transfusion was not associated with different rates or severity of postpartum hemorrhage. A few studies reported other potential maternal harms, including premature rupture of membranes and pulmonary embolism, and did not find differences by study group (**Appendix E Table 14**). However, these studies were underpowered for comparing rare outcomes. Nine other trials[87, 88, 91, 93, 94, 96, 102, 103, 105] reported comparisons between study groups in the rates of induction of labor, Cesarean deliveries, transfusions, or neonatal admissions, finding no significant differences, with the exception of one study[87] finding a greater number of Cesarean Sections in the placebo group compared with those taking aspirin, and two studies finding significantly more neonatal admissions in the placebo groups.[93, 103]

Treatment Adherence and Reasons for Trial Withdrawals

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 to treatment. Adherence, when reported, was generally high, although was 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 percent of their treatment medication; this number ranged from 72 to 88 percent. The mean ‘compliance’ index

(number of pills taken/number of days between visits X 100), as well as the median number of pills taken based on pill counts was also reported in select trials and ranged from 94 to 97 percent. 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.

KQ3a. Do the Harms of Aspirin Use to Prevent Preeclampsia Vary by Subpopulations Defined by Personal Characteristics or Preeclampsia Risk Factors?

We tested for differences in placental abruption or postpartum hemorrhage by aspirin dosage and timing among the included trials using meta-regression. No differences in harms related to the dosage of aspirin were seen in comparisons that included all trials included for these harms (**Appendix F Figure 6 and Figure 7**).

When comparing the effect estimates between studies of average-risk and increased-risk study populations, there were no statistically significant differences in estimates of placental abruption (p=0.41), postpartum hemorrhage (p=0.12), or intracranial fetal bleeding (p=0.34), although the effect estimates in the increased-risk population studies were closer to 1 in all cases (**Figure 9, Figure 10, Figure 11**).

Chapter 4. Discussion

Summary of Evidence

We identified three new trials eligible for this updated systematic review. The summaries of evidence and evaluations of the overall strength of evidence for each Key Question are provided in **Table 6**. There was reasonably consistent and precise evidence of effectiveness of daily low dose aspirin for prevention of fetal growth restriction and preterm birth among individuals at increased risk of preeclampsia. Preventing these outcomes has long-term implications for child and adult health. Newer evidence from a large trial contributed to greater precision for estimating a statistically significant association between aspirin and the prevention of perinatal mortality than in the 2014 review. Data from meta-analyses suggest that use of prophylactic low dose aspirin in women at increased risk for preeclampsia results in a 15 to 20 percent reduced risk of the disease and also for complications that lead to perinatal morbidity and mortality. The incidence of preeclampsia for participants assigned to placebo groups ranged widely, and this contributes to the range of absolute risk reductions related to disease incidence. The two largest trials, CLASP and MFMU-HR, reported similarly modest, statistically insignificant risk reductions of approximately 10 percent with absolute risk reductions near 2 percent. The more recent ASPRE trial obtained larger and statistically significant risk reductions, with absolute reductions for the incidence of preeclampsia closer to 2 percent and for preterm birth over 3 percent.

We estimated the number needed to treat (NNT) for preeclampsia, SGA/IUGR, and preterm birth using a range of values of incidence reported for the outcomes in the included evidence. The NNTs calculated from the midrange of study reported incidence rates for preterm birth and SGA/IUGR (17%) were similar, both around 30, but with wide confidence intervals (SGA/IUGR NNT = 33, 95% CI 18, 588 and preterm NNT= 29, 95% CI 18, 118) (**Table 7**). The NNT was estimated to be 20 or fewer at higher assumed levels of disease incidence for these outcomes, while at the lowest levels of risk, the NNT was 79 for SGA/IUGR and 50 for preterm birth. We estimated the NNT for preeclampsia prevention to be 74 (95% CI 44, 222) when the incidence of preeclampsia is nine percent, over twice the population average, and 51 (95% CI 31, 154) when the incidence is thirteen percent, approximately three times the population average.

Because aspirin use is known to affect pathways involving the inhibition of platelet aggregation, maternal and perinatal bleeding outcomes are important potential harms to consider. The addition of three new trials in the analysis of potential aspirin harms did not alter the previous null findings for the most consistently reported bleeding outcomes. Notably, however, the largest new trial, ASPRE, did not report postpartum hemorrhage outcomes, which limits the information available for assessing potential bleeding harms with a higher dosage than most trials (150mg). Bleeding outcomes, maternal hemorrhage and fetal intracranial bleeding (intraventricular and cerebral hemorrhage) were reported most consistently across all of the included trials. Given the lack of any statistically significant evidence of harms associated with daily low-dose aspirin use in pregnancy, we did not compute numbers needed to harm.

Maternal hemorrhage is the leading cause of severe maternal morbidity in the United States.[118] Data from the U.S.-based National inpatient sample indicate the incidence of postpartum hemorrhage has been increasing.[119] From 1993 to 2014, the number of delivery hospitalizations affected by postpartum hemorrhage requiring blood transfusion increased from 7.9/10,000 to 39.7/10,000. In 2009, postpartum hemorrhage accounted for slightly more than 10 percent of maternal deaths (1.7 per 100,000 live births).[7, 118, 120, 121] Having preeclampsia may increase a patient's risk for postpartum hemorrhage by various mechanisms, including prolonged induction of labor or coagulation abnormalities in patients with HELLP syndrome.[118, 122] The effect of aspirin prophylaxis during pregnancy on postpartum hemorrhage risk, defined in most studies as blood loss of 500 mL or more, was reported in eleven of the trials in this review, comprising results from over 23,000 participants. There was no increased risk of postpartum hemorrhage associated with aspirin use in trial populations at average or increased risk for preeclampsia. This null finding was accompanied by a reasonably precise confidence interval ranging from three percent reduced risk to nine percent increased risk, and no evidence of statistical heterogeneity. Postpartum blood loss may not be accurately measured in clinical practice, and the clinical significance of the 500mL threshold has been questioned, particularly for patients who receive cesarean section procedures.[123] A direct consequence of increased blood loss, such as incidence of maternal transfusion, would be a more informative outcome. The absence of differences in the available bleeding related outcomes, however, is reassuring for the daily regimen of 150mg or less of aspirin in pregnancy. The possibility of clinically significant differences for more rare, serious bleeding complications cannot be entirely ruled out, but because preeclampsia increases hemorrhage risk, effective aspirin prophylaxis could also reduce the occurrence of this harm.

Placental abruption, defined as premature separation of the placenta before delivery[124] is a condition which may be accompanied by maternal hemorrhage, disruption of blood flow to the fetus, need for emergent delivery, and/or stillbirth. The diagnosis of abruption is primarily made clinically and is less common than either preeclampsia or preterm birth, with national and international population-based studies suggesting abruption occurs in about 0.5 to 1.4 percent of pregnancies.[107-111] Placental abruption was a reported outcome in 13 trials, including 5 among average-risk individuals, comprising data on over 25,000 trial participants. The null finding for this intermediate outcome was less precisely estimated, and less consistent, than for postpartum hemorrhage, however, the lack of significant effect is consistent with the null findings for health outcomes that may result from placental abruption, including maternal and fetal hemorrhage and death. For less consistently reported harms such as congenital malformations, there was no evidence of an association with aspirin use, but the power to evaluate group differences for these outcomes was limited by their rarity.

Intraventricular hemorrhage (fetal intracranial bleeding) is the most common neurologic complication of prematurity, with risk for this outcome increasing with the degree of fetal prematurity at birth.[125] In a meta-analysis of 9 trials, the incidence of fetal intracranial bleeding did not differ between aspirin and placebo groups. The pooled effect confidence interval, which ranged from a 40 percent risk reduction to a 35 percent increase, was imprecise because the outcome was rare, however, the effect was in the direction of a reduced risk of fetal intracranial bleeding associated with prophylactic low dose aspirin, which parallels the observed reduction in risk of preterm birth.

Overall, meta-regression analyses did not support notable differences in effects for different study designs or population characteristics. Some benefit was observed across a range of aspirin dosages and timing, risk assessment approaches, and enrolled populations. Although there is some evidence for a greater benefit for perinatal health outcomes when aspirin is started earlier in pregnancy, results were inconsistent across outcomes, and comparisons may be confounded by other shared study features. There were too few studies included in the review to include multiple covariates in meta-regression, as would be needed to identify independent associations adjusted for other factors. In addition, some aspirin protocol features were too uncommon to compare across studies.

Comparison of Our Results With Findings From Other Systematic Reviews

The results of this review are consistent with findings from other systematic reviews including a recent Cochrane Collaboration review[123] and an older individual participant meta-analysis conducted by the Paris Collaborative Group (Paris IPD-MA) with trials published before the year 2006.[61, 126-129] Ten of the RCTs included in this review [89, 91, 92, 95, 97-100, 103, 107] were included in the Paris IPD-MA.[61] The Cochrane review included 77 trials conducted with 40,249 participants and their babies and incorporated available Paris IPD-MA data when available, pooling it with study level trial results that were more recently published. The Paris IPD-MA and Cochrane review both included trials of other anti-platelet medication, as well as aspirin combined with other medications. Despite differences in scope and approach, the Cochrane review results were mostly consistent with the findings of our review, with statistically significant benefits for prevention of preeclampsia, perinatal mortality, preterm birth, and small for gestational age, and null, less precisely estimated effects for risks of harm. There also were not statistically significant differences in aspirin effectiveness at different levels of preeclampsia risk in interaction tests conducted in the IPD-MA or the Cochrane review. The pooled effect magnitudes differed for some outcomes compared with our review findings. The most disparate result was for preterm birth, with the Cochrane analyses estimating a more modest statistically significant 9 percent risk reduction compared to the 19 percent risk reduction we estimated. The Cochrane review differed from ours in terms of included study design characteristics (e.g., included settings and medication regimens), preeclampsia risk levels (e.g., the Cochrane review included lower risk populations), risk of bias exclusions, and statistical methods (i.e., Cochrane review used fixed effects meta-analysis and incorporated individual level trial data). Likely a combination of these differences contributed to the differences in effect magnitudes, but the consistency of the finding of a beneficial effect of aspirin across important outcomes among all three reviews speaks to the strength of the evidence of aspirin for preeclampsia prevention in the large body of studies that has accrued to date.

The Cochrane review and Paris IPD-MA reported findings that were consistent with our review with respect to risks of harms associated with daily low dose aspirin use in pregnancy. None of the three reviews found statistically significant differences between groups in rates of postpartum hemorrhage ($\geq$ 500mL), placental abruption, fetal intraventricular hemorrhage, or other neonatal bleeding harms. In the Paris IDP-MA, there was a trend on the margin of statistical significance suggesting the possibility of higher risk of postpartum hemorrhage, based on evidence from 16

trials (RR 1.06, 95%CI 1.00, 1.13); the Cochrane review, which added results from 3 additional trials, showed a similar trend that was also not statistically significant. These results are difficult to interpret given the problems with the outcome definition and clinical significance of postpartum hemorrhage already discussed. Additionally, differences in the review scope, such as the inclusion of other antiplatelet medications and combined antithrombotic therapies in the other two systematic reviews could be associated with different risks for hemorrhage than aspirin alone. Overall, the large number of participants in trials evaluated in these reviews and ours do not provide a clear signal suggesting bleeding harms.

Consistent with our results, neither the Cochrane review nor the Paris IPD-MA found any definitive subgroup differences. As noted, the Paris IPD-MA results do not include evidence from more recent trials and was scoped more broadly than our current review.[61] Nevertheless, due to the strengths of an individual participant level of analysis for defining outcomes and assessing subgroup differences, the detailed findings warrant additional consideration. There was no evidence of subgroup differences tested with the Paris IPD-MA in effects by aspirin dosage, the timing of initiation of aspirin therapy, or according to characteristics and preeclampsia risks for study participants. The study found no difference in effectiveness for participants starting before 20 weeks of gestation compared to those starting treatment 20 weeks or later in pregnancy (p=0.24). Similarly, a secondary analysis of the data found no difference in effectiveness for preeclampsia prevention or for prevention of perinatal mortality when comparing treatment starting at less than 16 weeks of gestation to later initiation (p=0.98 and p=0.08, respectively).[127] The study also tested differences in intervention effects on preeclampsia prevention by aspirin dosage (<75 mg versus > 75mg) among trials that used aspirin only (excluding studies with other anti-platelet medications). The interaction test was not statistically significant (p=0.23). A secondary analysis comparing effects for dosages of ≤81mg compared with >81 mg doses suggest a possible trend toward greater risk reduction at higher aspirin doses (<81mg: RR = 0.92, 95%CI 0.85, 0.99; >81mg: RR = 0.74, 95%CI 0.60, 0.92), but the estimated effect confidence intervals overlap and a test for interaction was not reported.[129]

Overall, there is consistency across all major reviews of the accumulated evidence in finding that aspirin is effective for preventing preeclampsia and related outcomes, with no notable harms, and little indication of differences in effectiveness between particular regimens or risk populations. In general, there are no clear differences in effectiveness for different protocols or study populations supported by our review or other well-conducted comprehensive reviews on the topic.

Limitations

Exclusions for Publication Language and Study Setting

Our search was limited to English language literature, and only trials conducted in settings with very high Human Development Index scores were included. Large trials conducted in other settings could provide additional relevant information, but other reviews without this exclusion have not found substantively different results.[61, 123] A large, recently published multicountry trial enrolled average-risk nulliparous participants from seven community sites in the Democratic

Republic of Congo, Guatemala, Kenya, Pakistan, and Zambia from March 2016 to June 2018 and randomized 11,976 pregnant individuals to 81mg of aspirin or placebo between 6/0 weeks and 13/6 weeks of gestation.[63] Had we not limited our review by setting, this trial would have contributed to our analysis of Key Question 3 (evaluating harms) and would not have changed our main conclusions: the trial did not find any study group differences in a large set of reported adverse events and potential harms, including postpartum hemorrhage and congenital malformations.

Small-Study Effects

We found evidence of small-study effects for several outcomes. This suggests that smaller null or negative studies may not be present in the published literature or that smaller trials have systematic differences in conduct and methods than larger trials, skewing pooled results toward an overestimation of effectiveness. We conducted sensitivity analyses using fixed effects models, given the propensity for random effects models to amplify small-study effects. These analyses demonstrated small differences in the magnitude of effects for various outcomes, though all effects remained statistically significant. Different statistical approaches for estimating pooled effects and testing subgroup comparisons, however, cannot fully address some limitations in the data. For example, the two largest studies used the same low aspirin dosage (60mg) and enrolled the majority of their study participants after 16 weeks of gestation. The MFMU-HR trial additionally instructed participants to cease aspirin use if preeclampsia developed. Thus, the small-study effects seen in the evidence cannot be entirely disentangled from other features of the included studies. It is not possible to determine which factors – those external to the evidence such as publication bias, or those specific to the design of the included studies – are responsible for small-study effects, and both types of factors could contribute.

Confounding of Aspirin Initiation Timing Effects

The most recent Cochrane review[123] and the Paris IPD-MA[61] did not find evidence of differences in aspirin effectiveness associated with the timing of aspirin use during pregnancy when analyzing effects with initiation before 20 weeks of gestation compared to later start times using study level data and individual participant data. Our subgroup findings agree with and were similarly interpreted. Other systematic reviews focused on selected subsets of the available trial evidence have reported significant differences in effectiveness related to the timing of aspirin initiation using a cutpoint of 16 weeks of gestation. This could be due to problems with subgroup comparisons at the study level, which are subject to more serious bias and confounding than individual level comparisons. A secondary analysis of the IPD-MA data examining effects for aspirin initiated before 16 weeks of gestation or started later also did not show a statistically significant differences in the effects.[127] Given the inconsistency in evidence for timing effects across outcomes and the potential for confounding to influence subgroup comparisons, there is not clear evidence that aspirin is more effective when aspirin is started before 16 weeks of gestation. This was true in our current review of aspirin effectiveness focused on increased-risk populations, and in the Cochrane review that includes a broader literature along with results from the Paris IPD-MA.[123] Further research is needed to examine the possibility that earlier initiation

may lead to greater benefit for some individuals, but it appears that even those presenting for prenatal care beyond 16 weeks can derive a benefit from daily low-dose aspirin.

Observational Evidence Exclusions

The 2014 USPSTF review included two observational cohort studies that were not included in this update. These studies examined any aspirin use during pregnancy and reported null findings for the potentially harmful outcomes considered, miscarriage and cryptorchidism.[108, 109] The current review adopted a narrower approach to assessing observational studies for inclusion, given the size and maturity of the trial evidence on the topic, and the unique aspirin protocol used in trials that is not found in large observational studies examining outcomes associated with aspirin use at any time or dosage during pregnancy for a range of possible indications. We would have included any observational cohort studies that reported harms outcomes among women taking daily aspirin for preeclampsia prevention, but none were identified in our literature search.

A large body of observational evidence has examined whether aspirin and nonsteroidal anti-inflammatory drugs increase the risk of birth defects. Findings are somewhat mixed; most studies report no association or unclear results,[130-133] but there are important limitations to the literature. In studies of aspirin for preeclampsia prevention, a low dosage is initiated after the first trimester, when embryogenesis is complete. Therefore, some types of birth defects would not be expected to occur. Most observational studies cannot adjust for the timing, dosage, or indication for aspirin exposure. Ascertainment bias and unmeasured confounding also limit conclusions that can be drawn even from large, well conducted case-control studies.[132] From the observational evidence, there are not clear or consistent associations found between aspirin and birth defects. If present, such effects would be very small in order to have escaped detection in the observational and trial data available on this topic.

Adherence

Our review reported and meta-analyzed results only from intention to treat analyses, in accordance with methodological guidance for conducting systematic reviews and best practices for interpreting trial evidence.[84, 134] There is evidence in the literature from secondary analyses of trials that differences in adherence to daily aspirin use may contribute to the differences in effectiveness observed in the trial literature, and that efficacy of aspirin use is considerably higher than effectiveness.[59, 135] We did not analyze data from trials based on adherence to treatment, and from a pragmatic standpoint, the estimates we provide in this review are more representative of the effects that might be expected in clinical populations with varying levels of adherence to a recommended preventive intervention. The MFMU-HR trial, which reported modest null effects of prophylaxis, reported that 80 percent of participants reported taking at least 80 percent of their aspirin tablets, and found no differences in effectiveness based on self-reported adherence.[99] However, there is evidence from a multicenter observational cohort study that adherence to aspirin (100mg or 150mg) greater than 90 percent (assessed with blood test) compared with any lower level of adherence resulted in statistically significant differences in its effectiveness for preeclampsia and perinatal health outcomes.[136] An accompanying editorial noted that adherence could be affected by the methods a trial takes to determine risk and to

assess medication adherence, and these adherence differences could account for differences in effect magnitudes seen across aspirin trials.[137] Similarly, there is evidence that adherence to aspirin prophylaxis may be relatively low in pregnancy, with somewhat higher levels for those concerned about their risk for preeclampsia.[138] These studies highlight the potential importance of further research to understand the importance of adherence for obtaining preventive benefits.

Identifying Patients at Increased Risk for Preeclampsia

Currently, there is limited evidence about the best approach for identifying women at risk of preeclampsia.[139, 140] Trials varied in their approaches for identifying participants and in the exclusion criteria they used. A little over half of the included trials used multiple risk factors to identify women at risk for preeclampsia, and of the trials that relied on a single risk factor, only two relied on the same one (abnormal doppler ultrasound readings).[90, 103]Consequently, baseline characteristics of the study populations varied significantly, resulting in a broad range of preeclampsia incidence rates in the control groups (4 - 30%) (**Table 4**). Some of the tests used to identify women at risk of developing preeclampsia in the older trials were conducted in the second trimester of pregnancy (some as late as 26-28 weeks of gestation) and are not currently used in clinical practice (i.e., hemoglobin >13.2 g/dL, maternal roll over test resulting in rise of diastolic blood pressure >15 mg Hg above baseline, and increased blood pressure response to angiotensin II infusion).[87, 89, 96]

Study level subgroup comparisons tested in this review did not find differences in aspirin effectiveness based on the approach taken for identifying women at increased risk of preeclampsia. While studies that used clinical risk factors in conjunction with clinical tests or imaging consistently recruited populations with high incidence of preeclampsia (18 and 23%),[89, 104] several studies using clinical risk factors alone achieved similarly high levels of preeclampsia incidence ranging from 8 percent to 20 percent (**Table 4**).[57, 93-95, 98, 99, 101] Subgroup analyses did not show any differences in the effectiveness of aspirin between studies that used clinical history risk factors alone to identify women at increased risk compared to those that incorporated clinical tests or imaging, nor did the effectiveness of aspirin vary by the incidence of preeclampsia in the study control group (≤12% vs >12%) (**Table 4**). However, subgroup comparisons were limited by the diversity of approaches taken and the inability to account for potential confounding from other study characteristics (e.g., aspirin protocol) with the available trials.

The most recently published RCT of aspirin for prevention of preeclampsia, the ASPRE trial, was the only trial to use a previously developed, externally validated risk prediction model for predicting preeclampsia.[141] The model was used to assess risk of preeclampsia leading to preterm birth in participants with singleton pregnancies at 11 to 12 weeks of gestation. The prediction algorithm draws on Bayesian statistics to first estimate risk based on several clinical history characteristics; weight, height, maternal age, race/ethnicity, previous preeclampsia, family history of preeclampsia, chronic hypertension, diabetes type 1 or 2, systemic lupus erythematosus or antiphospholipid syndrome, and conception by *in vitro* fertilization. This was then supplemented with serum biomarker tests (pregnancy associated plasma protein-A and placental growth factor), mean arterial pressure, and Doppler ultrasound readings of the uterine

artery pulsatility index. Using this algorithm, the trial identified a study population where 11 percent of control group participants developed preeclampsia, about 3 times the incidence in the general population. It is not clear whether the greater effectiveness of aspirin seen in the ASPRE trial relative to other large trials can be attributed to the risk assessment approach, and how much is due to other differences, such as the higher aspirin dosage, or the early initiation of aspirin at 12 to 13 weeks of gestation and continuation until 36 weeks or onset of labor. Whether the algorithm identifies a population particularly responsive to aspirin cannot be determined without further comparative research.[141]

The MFMU-HR trial conducted stratified enrollment and analyses to test whether aspirin was more effective for certain risk groups relative to others. The trial defined four risk categories: those at risk of diabetes, chronic hypertension, and multifetal gestation, and those with a previous pregnancy affected by preeclampsia. There were no statistically significant effects of aspirin for preventing preeclampsia or other health outcomes in the trial overall or within risk category subgroups. All risk groups except the chronic hypertension category had similarly modest reductions in preeclampsia risk (approximately 10%). In the chronic hypertension risk category, more participants in the aspirin treatment group developed preeclampsia than in the placebo group, but the estimate was imprecise and comparisons between groups were statistically underpowered.

Despite ongoing efforts to develop a screening test or prediction algorithm that can be used in early pregnancy to identify individuals who are likely to develop preeclampsia, clinical history taking remains a practical and commonly-used approach that can select populations with higher incidence of preeclampsia than the population average. Aspirin was effective across a range of populations at different levels of risk who were selected based on a variety of approaches. Risk prediction models that include uterine artery Doppler ultrasound readings and biochemical markers from serum testing alongside patient characteristics are more resource-intensive and difficult to clinically implement but may hold potential. The most widely tested prediction models have yet to be externally validated, and require further evaluation to determine their clinical effectiveness and value to support widespread use across a range of populations.[1, 40, 66]

Some researchers have advocated for broader clinical uptake of the algorithm used in the ASPRE trial for selecting patients to aspirin prophylaxis,[142] including a recommendation from the International Federation of Gynecology and Obstetrics (FIGO) (**Table 1**) (co-authored by the model developers). Others have questioned this based on practical shortcomings and knowledge gaps, highlighting its limited suitability to general clinical practice for now.[1, 40, 66, 139, 143] Many pregnant individuals would not be eligible for screening, including those entering prenatal care beyond 12 weeks of gestation or who are pregnant with twins or more. It is also unclear what level and attributes of test performance are most important assigning aspirin prophylaxis, given the low risk of the intervention. For low dose aspirin prophylaxis, optimizing specificity rather than sensitivity (higher false positive rate) might be reasonable. Validated prediction tools with strong test performance attributes would be very valuable for improving prenatal care and early intervention if they were able to identify those who are very likely to develop preeclampsia, but may be less important for identifying a clinical population in routine care that might benefit from aspirin prophylaxis. A review comparing the test performance attributes of development and validation models for the predictive model found significant differences in accuracy depending

on the cohort used, leading the authors to conclude that more effort should be dedicated to refinement and validation of models as well as studies evaluating whether model use improves clinical care and outcomes.[144]

Comparisons of clinical risk assessment approaches recommended by ACOG, NICE, and USPSTF to formal prediction algorithms for identifying populations at increased risk that could benefit from aspirin to prevent preeclampsia have highlighted differences in test performance characteristics. Not surprisingly, these comparisons show that prediction models designed to optimize accuracy have greater predictive value. As others have noted,[143] however, while accurate prediction of preterm preeclampsia in singleton pregnancy is important for many purposes, lengthy clinical risk assessment procedures may not represent the most efficient, practical, or effective way to ensure that recommendations to use aspirin during pregnancy reach the broad population of individuals that could potentially benefit from use. Further research is needed to determine whether there is a discernable difference between aspirin effectiveness for individuals identified using a prediction model and those identified using clinical history risk factors in routine prenatal care. Implementation trials comparing these strategies in real-world settings would be particularly valuable, especially if designed to address questions related to aspirin timing as well. It would be especially important to further strengthen approaches for identifying individuals that are most likely to manifest severe features of preeclampsia that lead to more serious morbidity and mortality.

In addition to the trial evidence included in this review, several reviews and large cohort studies provide evidence on important risk factors for preeclampsia. These were cited in the previous USPSTF recommendation statement[69] and were referenced in the recent ACOG recommendation for aspirin to prevent preeclampsia.[66, 145] A similar set of risk factors were cited in the updated National Institute for Health and Clinical Excellence recommendation for the United Kingdom **(Table 1)**. These include several risk factors known to be independently associated with the highest likelihoods of developing preeclampsia: history of preeclampsia, multifetal gestation, chronic hypertension, and type 1 or type 2 diabetes. Other, more moderate risk factors are associated with an increased risk, such as maternal age over 35 and nulliparity, but are inconsistently or only modestly independently associated with preeclampsia risk. More than one moderate risk factor, occurring in the same individual, however, would be expected to identify increased risk for preeclampsia similar to levels observed in the control groups of the trials that established intervention effectiveness.

There has been no change in the main clinical risk factors associated with preeclampsia that would be reasonable to consider for identifying similar-risk populations to those included in the 2014 USPSTF review. Clinical risk factors included in the risk predication model used in the ASPRE trial were similar to those recommended by NICE, ACOG, and the USPSTF, with the exception of *in vitro* conception. This clinical history could be incorporated into current clinical assessment practices, although only a small fraction of participants in aspirin trials had this risk factor. There are also other risk factors not included in the current guidelines that may also be associated with a moderate risk for preeclampsia and warrant further research both in terms of establishing the potential association and evaluating whether aspirin prophylaxis would be beneficial. These include high altitude residence, exposure to air pollution,[146] sleep disordered breathing during pregnancy,[147, 148] and migraine headaches.[149] **Table 8** provides a list of

established clinical history risk factors that can be used alongside clinical judgment of risk to identify increased-risk populations that are likely to approximate the population included in the trials on aspirin prophylaxis reviewed here.

Having had a previous pregnancy complicated by a hypertensive disorder is a consistent, well-established risk factor for preeclampsia, and there is some evidence that this risk factor identifies a population that may be particularly responsive to aspirin prophylaxis.[61] Additionally, a history of preeclampsia may be associated with an increased risk of having an SGA infant, even if preeclampsia does not occur, highlighting the importance of this risk factor for identifying individuals that could benefit from aspirin prophylaxis.[150] Of course, for nulliparous individuals, this important pregnancy history risk factor is unavailable. First pregnancies are at somewhat greater risk for preeclampsia than later pregnancies; as a result, the population-attributable risk is high for nulliparous patients.[38] Studies we reviewed that enrolled general nulliparous populations without additional risk factors had incidence of preeclampsia below or just above the population average in their control groups.[91, 92, 100, 102, 105] Efforts to develop prediction algorithms focused on nulliparous populations have had limited success,[139, 151-153] and generally have not performed better than recommended approaches to clinical risk assessment. The addition of serum markers and imaging findings may improve performance,[39, 154] but further validation in nulliparous populations and comparison to other risk assessment approaches is needed. Research to inform risk assessment for those having a first pregnancy is needed to ensure that those who would benefit from aspirin prophylaxis are identified.

Finally, there is a developing discussion in the literature[155-157] as to whether low dose aspirin prophylaxis should be considered for all pregnant women given challenges predicting who will develop preeclampsia, particularly among nulliparous individuals, and the absence of any clear evidence of harms.[156, 158] The inclusion of low-risk populations in systematic reviews tends to result in more modest effect estimates compared to reviews focused on higher risk populations, but in the most recent Cochrane review, there was not a statistically significant difference in aspirin effectiveness between different levels of risk.[123] We also did not find differences in the main harms outcomes we evaluated when comparing the effects between studies conducted among average-risk (mainly nulliparous) populations and studies with increased-risk study populations. With additional research, it may become reasonable to consider a shift away from identifying increased-risk populations toward identifying low-risk populations that are unlikely to derive any benefit from aspirin prophylaxis for preeclampsia prevention. This will require more evidence on the long-term safety and benefits of aspirin prophylaxis to support intervention involving larger numbers needed to treat.

Evidence Gaps and Future Research

In addition to the gaps around identifying patients at increased risk for preeclampsia and most likely to have more severe complications (detailed above), there are a number of other evidence gaps that call for future research. The literature we reviewed is limited for the purposes of identifying the specific aspirin protocol (dosage, timing, continuation, time of day) that is likely to have the greatest benefit, and the risk population that is most likely to benefit. In addition, the long-term risks and benefits of low dose aspirin for the mother or her child are uncertain, as the

included trials have not reported long-term outcomes. The studies we reviewed varied considerably on these characteristics, in addition to having differences in excluded populations and sample size. No studies reported head-to-head comparisons of different protocols or risk assessment strategies, and only one trial was designed to compare effectiveness for different risk populations, and it was underpowered for drawing conclusions. Interaction tests for subgroup differences within trials were uncommon, and, when available, did not generally identify differences in effectiveness by the factors examined. Meta-analysis results for some outcomes, and especially for making subgroup comparisons, were limited by low numbers of included studies and low event rates for some outcomes. Comparisons between studies in meta-regression were generally not statistically significant. When differences were seen, as for the timing of aspirin initiation on preterm birth prevention, the limited number of studies compared and potential for confounding prevented us from drawing strong conclusions. For example, only one study evaluated differences in the action of aspirin depending on the time of day it was taken,[57] providing limited evidence that effectiveness may be greater when aspirin is taken at least 8 hours after waking or at bedtime. Further research is needed to explore this possibility. Overall, the low to moderate statistical heterogeneity and consistency of effects across a range of outcomes supports the conclusion of this review, that low dose aspirin is effective for preventing preeclampsia and related perinatal morbidity and mortality for individuals at increased risk for preeclampsia. More research will be needed to determine the optimal aspirin protocol and identify key populations most likely to obtain benefits.

Applicability of Evidence and Health Equity

The included studies in this review ranged from explanatory to pragmatic in their design features but were all randomized trials and therefore represent a subset of the larger population of pregnant individuals who were willing to undergo randomization to daily medication use during pregnancy. The effectiveness of the intervention, due to differences in adherence or the health status between participants and the general population, may not match what has been found in clinical trials.

The majority of participants in the included trials were White, limiting the generalizability of results to racially and ethnically diverse populations at risk for preeclampsia. Only the two United States trials, the MFMU-HR trial,[99] which recruited women at increased risk for developing preeclampsia, and the MFMU-LR trial,[92] in average-risk nulliparous individuals, enrolled substantial numbers of Black and Latinx study participants; none of the included studies enrolled significant numbers of other minority racial or ethnic groups. Thus, the evidence is limited for assessing whether there could be racial or ethnic differences in the effectiveness or potential harms of aspirin in pregnancy. This is a troubling in light of the greater morbidity from preeclampsia experienced by Black women in the United States compared to other racial and ethnic groups.[11] More than half the participants enrolled in MFMU-HR were Black, and the trial did not find a difference in aspirin effectiveness by race/ethnicity (coded as ‘nonWhite’ versus ‘White’), but the low magnitude of effects in this trial limited the comparison. Racial/ethnic differences in aspirin effectiveness or harms could exist, owing to the prevalence of different risk factors in different racial groups, environment/gene interactions, or other factors. Such differences could contribute to heterogeneity in the effect magnitudes observed in the evidence

we reviewed. Given the troubling disparities in maternal health and birth outcomes documented among Black women in the United States,[11, 159, 160] research is urgently needed to address this evidence gap.

A retrospective cohort study of births among "Hispanic" and "African-American" individuals with a history of preeclampsia provides evidence that benefits seen in the trials included in this review can be obtained in routine care settings. The study compared preeclampsia recurrence before and after the release of the 2014 USPSTF recommendation for aspirin prophylaxis.[64] Adjusted analyses indicated 30 percent reduced recurrence of preeclampsia, despite an increase in rates of pregestational diabetes over the study period (a significant risk factor for preeclampsia). Although the observational study design is subject to risk of bias from historical trends and other unmeasured confounding, it supports the applicability of trial evidence synthesized in this review on to routine care provided in clinical settings serving diverse populations. Nevertheless, further research on implementation will be needed to ensure that effective interventions are equitably distributed, as health disparities in preeclampsia may be further exacerbated by unequal access high quality antenatal health care where effective interventions are implemented in practice.

Chronic and Gestational Hypertension

A recent study of over 44 million deliveries in the Nationwide Inpatient Sample dataset found that the incidence of hypertensive disorders in pregnancy increased from 8.4 percent in 2004 to 10.9 percent in 2014, with the largest increases seen in the categories of gestational hypertension and chronic hypertension. Of note, women with chronic hypertension without preeclampsia had higher risks of cardiovascular events (myocardial infarction and arrhythmia) than women with preeclampsia without hypertension. Women with chronic hypertension as well as preeclampsia had the highest risk of adverse outcomes (including much higher risks of preterm birth, stillbirth, and stroke).[161]

The trials included in our review also showed higher preeclampsia incidence for participants entering the study with elevated blood pressure than those without elevated blood pressure, when this was reported. Participants with chronic hypertension enrolled in the MFMU-HR trial had the highest rates of preeclampsia, and nearly the same proportion of participants developed preeclampsia in the aspirin group as in the placebo group, 25 and 26 percent, respectively. A subgroup analysis in the ASPRE trial suggested a higher risk of preterm birth with preeclampsia among women with chronic hypertension in the aspirin group than in similar women assigned to placebo:[59] a test for an interaction between hypertension status and treatment group was on the margin of statistical significance. These two trials suggest that aspirin may not be effective for individuals with hypertension diagnosed before pregnancy, but the results are inconclusive. In addition, the trial literature we reviewed was limited for determining whether a diagnosis of chronic hypertension using the AHA's revised lower systolic and diastolic blood pressure cut points of 130 and 80, respectively, should be incorporated when identifying women at risk of preeclampsia.[162] In a systematic review of cohort studies evaluating risk factors for preeclampsia, a systolic blood pressure at the initial visit of $\geq$130 mm Hg vs <130 was associated with an unadjusted relative risk of preeclampsia of 2.37 (1.78 to 3.15) and a diastolic blood pressure of $\geq$

80 versus <80 was associated with a unadjusted relative risk of preeclampsia of 1.38 (1.01 to 1.87).[163]

There is limited, but suggestive evidence from secondary analysis of data from the MFMU-HR trial that for individuals with stage 1 hypertension at baseline (less than 26 weeks of gestation) that were not previously hypertensive, aspirin may be more beneficial for certain risk groups.[164] Though the analysis had limitations, it suggested that the presence of stage 1 hypertension before 26 weeks of gestation was associated with later preeclampsia incidence, and that aspirin was more effective for preeclampsia prevention among individuals with this level of hypertension than among those without. A similar analysis of the entire study population reported in the primary MFMU-HR trial publication, however, found similar aspirin effectiveness for participants who were not hypertensive at baseline but had systolic blood pressure of 120 to 134 mmHg and those who were normotensive at study entry (before 26 weeks of gestation).[99] A trial included for harms in this review, also conducted in racially and ethnically diverse patients recruited from MFMU network[92] sites, found that aspirin may be effective in healthy nullipara with SBP 120-134 mm Hg at baseline, whereas no difference between aspirin and placebo was found for lower baseline blood pressure levels.[99] Among the risk group in MFMU-HR with chronic hypertension at study entry, who were excluded from the secondary analysis described above, there were more cases of preeclampsia in the aspirin group than the control group.

Taken together, these findings suggest that those with chronic hypertension (now considered stage 2 chronic hypertension) may be less responsive to aspirin prophylaxis, while individuals without a history of chronic hypertension who are newly identified as having stage 1 hypertension early in pregnancy may be more likely to benefit than individuals with no hypertension. Future research is needed to determine whether there is a subgroup of women with pre-existing hypertension, perhaps those with a recent diagnosis at a lower diagnostic cut point, who may benefit from aspirin therapy. The limited data leave it unclear whether the risk of superimposed preeclampsia may be mitigated by aspirin prophylaxis, especially among women with stage 2 hypertension, but no studies have been adequately powered to examine this hypothesis.

Another area of uncertainty is the benefit of aspirin for the prevention of gestational hypertension in the absence of preeclampsia. We attempted to address this question by pooling all cases of gestational hypertension from studies that provided the outcome. Our meta-analysis found that the direction of risk reduction was the same for gestational hypertension as for preeclampsia, but even though effect magnitude was greater, the estimate did not achieve statistical significance. One challenge in assessing gestational hypertension from the available RCT data is that the presence of this condition is not commonly reported in a way that would allow us to identify participants who were diagnosed with preeclampsia after an initial diagnosis of gestational hypertension. Thus, if aspirin reduces the likelihood that gestational hypertension will transition to preeclampsia, there could be more cases of gestational hypertension (rather than preeclampsia) reported in the intervention group. Aspirin might also reduce the risk for gestational hypertension. Given that gestational hypertension and preeclampsia are now treated the same at term (i.e. delivery is recommended at 37 weeks of gestation for both conditions),[1] we conducted an additional exploratory analysis assessing whether aspirin was effective for reducing the risk of hypertensive disorders of pregnancy as a whole in trials reporting adequate data. We found a

significant risk reduction in the aspirin condition, supporting the possibility that aspirin may be useful for prevention of both gestational hypertension and preeclampsia. Further confirmatory research is needed.

Obesity

One question for which current trial data are limited is whether the dosing of aspirin for the prevention of preeclampsia should differ for women with a higher body mass index. Only two of the included trials performed analyses stratified by BMI to examine the differential impact of LDA for prevention of preeclampsia (MFMU-HR, 60 mg) and prevention of preeclampsia with preterm birth (ASPRE, 150 mg) and found no significant differences by BMI category. One hypothesis for why the dose of aspirin may need to be different for women with obesity is that the degree of thromboxane inhibition achieved at a given dose may vary by BMI. To examine whether aspirin is associated with less thromboxane inhibition among women with obesity, a subsequent secondary analysis was conducted in a subgroup of 1002 of the original 2539 ppts the MFMU-HR trial.[165] Women in the cohort were stratified by BMI (obese ≥30 kg/m^2 vs nonobese <30 kg/m^2). The primary outcome was rate of complete thromboxane B2 (TXB2) inhibition, defined as undetectable TXB2 levels <0.01 ng/mL and the secondary outcomes were rates of preeclampsia at any gestational age and preeclampsia with preterm delivery <37 weeks in women with and without undetectable TXB2 levels. Women with obesity assigned to LDA had statistically significant lower rates of undetectable TXB2 levels in the second trimester (39.4% vs 30.2%; P =.04), but not during the third trimester (41.4% vs 32.9%; P=.12), and were substantially less likely to have undetectable levels of TXB2 at both time points (30.6% vs 17.7%; P = .010). However, there were no differences in rates of preeclampsia in women receiving LDA with undetectable TXB2 levels in the second trimester (17.2% vs 20.8%; P=.34), third trimester (16.4%vs 19.7%; P=.46), or at both time points (16.5% vs 17.5%; P = .83), and there were no differences in rates of preeclampsia with delivery less than 37 weeks in women with undetectable TXB2 levels in the second trimester (9.9% vs 9.2%; P=.71), third trimester (4.5% vs 7.4%; P = .27), or at both time points (5.1% vs 6.3%; P =.83).

In summary, while there appears to be a differential effect of aspirin on thromboxane inhibition among women with obesity, this does not appear to result in a differential impact on outcomes, although trial data examining the effect of BMI are limited.

Identifying Serious Harms

The challenge in identifying potentially serious harms is apparent when considering the outcome of clinically significant postpartum hemorrhage. As noted above, the trial evidence most commonly used a measure of 500mL or more of blood loss to define postpartum hemorrhage, but this number is of questionable clinical significance.[123] In 2014, after all but two of the studies included in this review were published, the national reVITALize initiative[166] worked to standardize obstetric data definitions and redefined postpartum hemorrhage as a cumulative blood loss greater than or equal to 1,000 mL, or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (including intrapartum loss) regardless of

route of delivery.[167] This new definition is believed to be more clinically meaningful and has been adopted by the American College of Obstetrics & Gynecology.[118] Future trials may benefit from adoption of an outcome measure consistent with this definition to better assess whether there are meaningful differences in postpartum hemorrhage rates associated with aspirin to prevent preeclampsia. In the meantime, the possibility of clinically significant differences for more rare, serious implications cannot be entirely ruled out.

Longer-Term Health Outcomes

It is possible that there are longer-term child and adult health implications associated with preeclampsia and/or its prevention with aspirin prophylaxis. Only one included trial reported followup beyond the perinatal period:[95] a subset of the children of trial participants were assessed at 18 months of age.[113] While this study was reassuring with regard to the lack of developmental harms in toddlerhood, there remains a need for longer-term followup, to assess potential harms and potential benefits of intervention. A growing body of research suggests that exposure to preeclampsia in utero may be harmful to future health. Longer-term trial followup could evaluate the possibility that prevention of preeclampsia with aspirin may reduce offspring risk of cardiovascular disease[168, 169] as well as for neurocognitive conditions such as attention deficit hyperactivity disorder,[170, 171] autism spectrum disorder, epilepsy, intellectual disability, and vision or hearing loss.[172]

Followup on trial participants would similarly have the potential to shed light on whether prevention of preeclampsia during pregnancy has long-term health implications for mothers. A number of studies have found associations between preeclampsia and long-term cardiovascular health outcomes.[173, 174] Estimates suggest a possible doubling or tripling of cardiovascular disease risk in women who have had preeclampsia during any pregnancy,[175, 176] as well as an increased risk for early stroke (before age 60).[177] Risks may be considerably higher in women who had early-onset preeclampsia.[178] Subclinical brain and endothelial damage may occur from the cardiovascular strain and metabolic effects of preeclampsia.[174, 179-181] It is unclear whether these changes cause the observed increased long-term cardiovascular disease and mortality risk associated with a history of preeclampsia, or if differences arise from underlying risk profiles among women that potentiate the development of both of these short- and long-term outcomes.[182] Further research, including extended followup on aspirin trials, could shed light on the mechanisms and causal pathways between preeclampsia prevention and longer-term health.[179]

Conclusions

Few new studies have been published since the previous review conducted for the USPSTF. The addition of a large trial strengthened the evidence for the effectiveness of low dose aspirin for preventing preeclampsia and reducing the risk of SGA/IUGR, preterm birth, and perinatal mortality, across a range of aspirin protocols and increased-risk populations. Data from over 25,000 individuals randomized to daily aspirin use for preeclampsia prevention do not suggest that there are serious harms associated with low dose aspirin use for this purpose during

pregnancy. The evidence included in this review cannot rule out rare harms from low dose aspirin use during pregnancy, although findings are reassuringly consistent with the findings of large registry and cohort studies (not included in this review) examining potential harms of aspirin exposure at any gestation, at any dose, and for any indication. The effectiveness of aspirin is supported across a range of risk assessment strategies, aspirin dosages, and protocols regarding when during pregnancy to begin taking aspirin. Further research is needed to address gaps in the research related to potential variability in the effectiveness of aspirin that could not be resolved from subgroup comparisons in the existing trial evidence on this topic. Even if aspirin has only modest effectiveness for improving the pregnancy outcomes evaluated, their seriousness means that the intervention could result in important benefits to population health. Finally, the benefits of aspirin prophylaxis may not always reach those at risk, especially populations with limited access to high quality prenatal care. Implementing strategies that promote equitable access to this intervention could help address preeclampsia health inequities, especially those observed for Black women in the United States.

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Figure 1. Analytic Framework

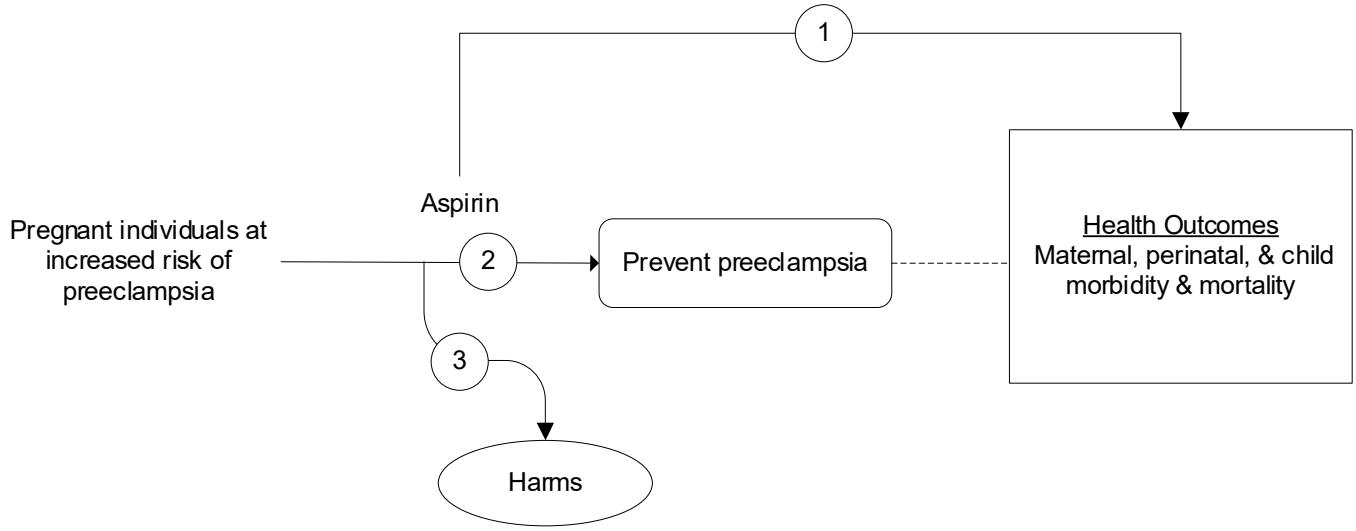
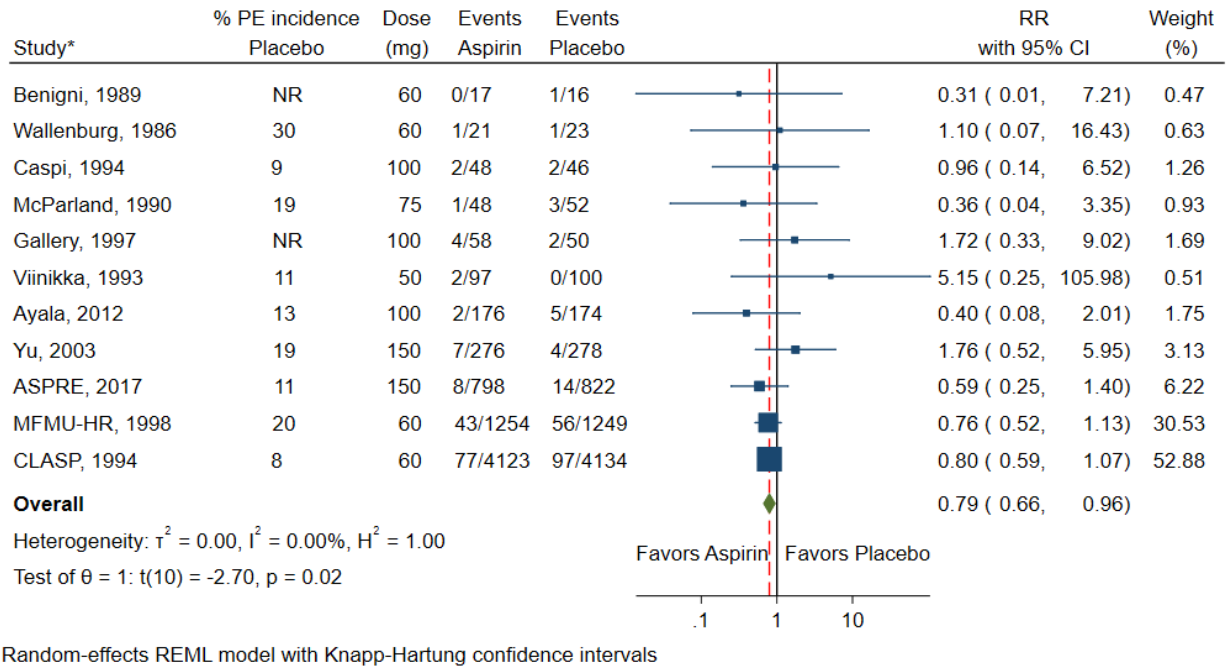


Figure 2. Perinatal Mortality, Sorted by Study Size

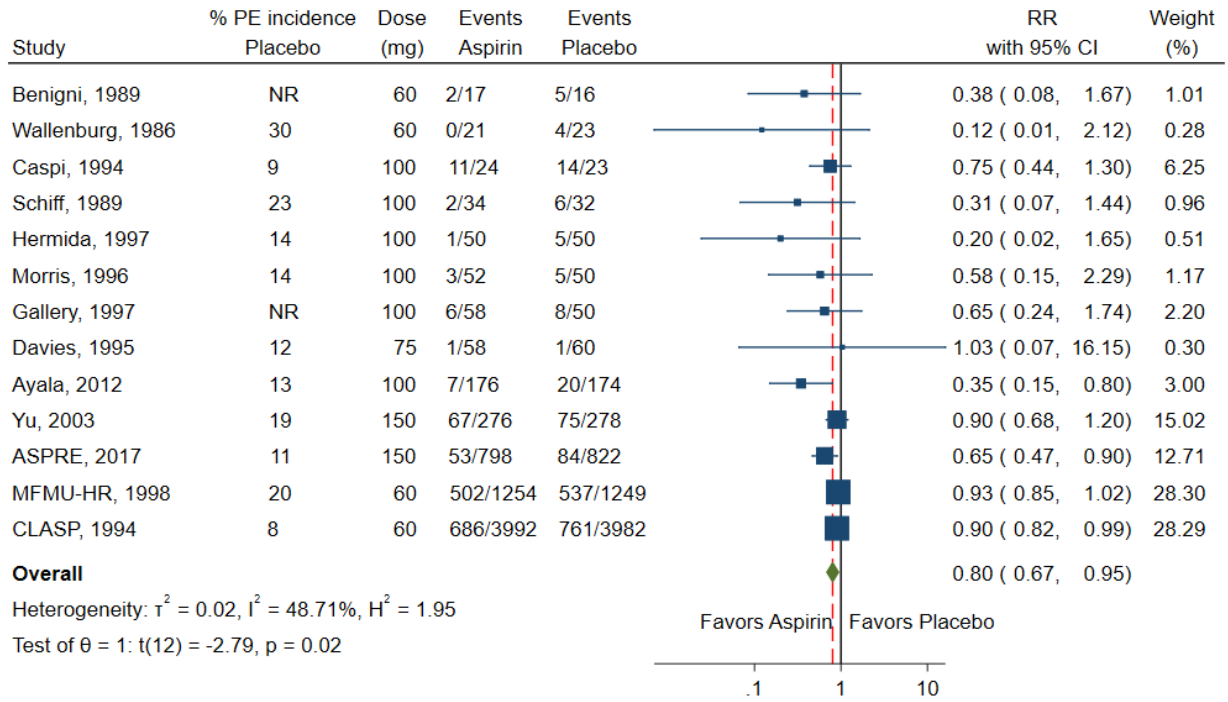


Random-effects REML model with Knapp-Hartung confidence intervals

Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

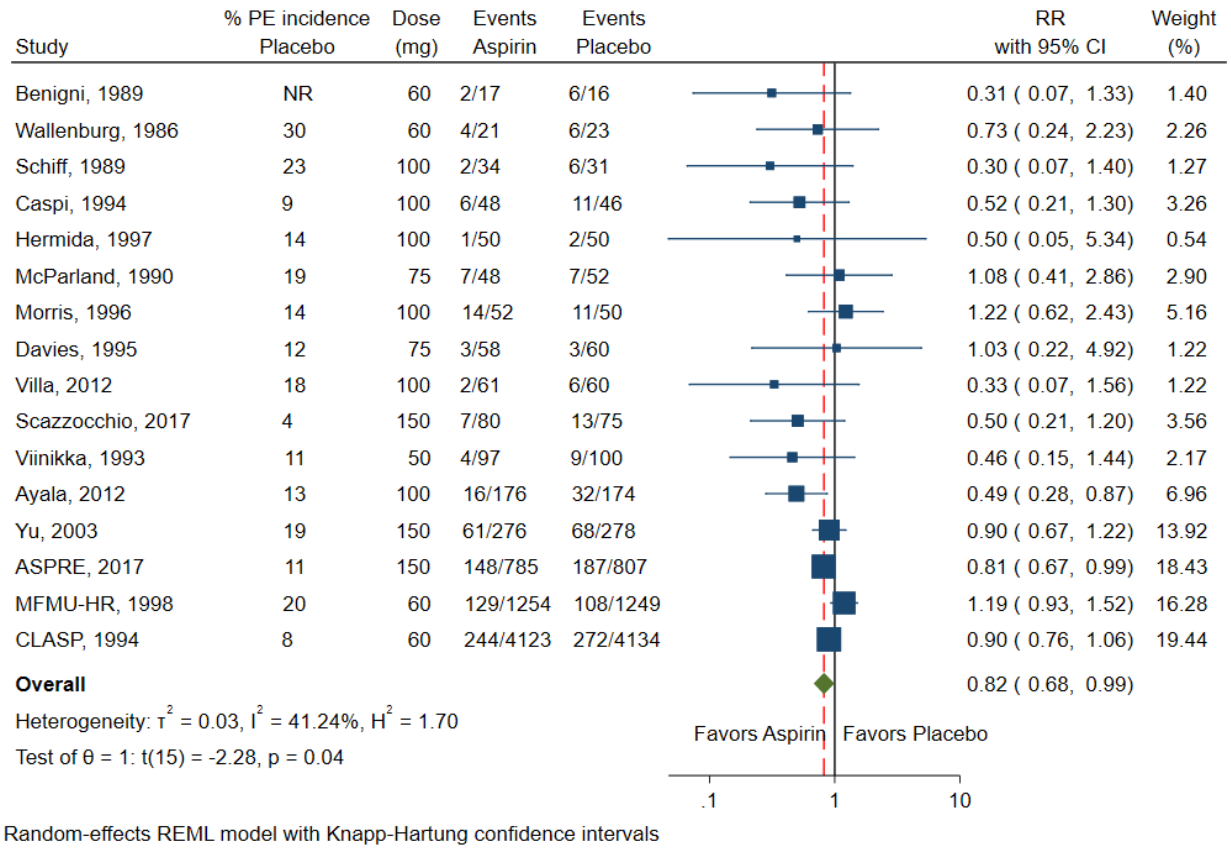
*Excluded 4 studies with both arms having zero events.

Figure 3. Preterm Birth Before 37 Weeks' Gestation, Sorted by Study Size



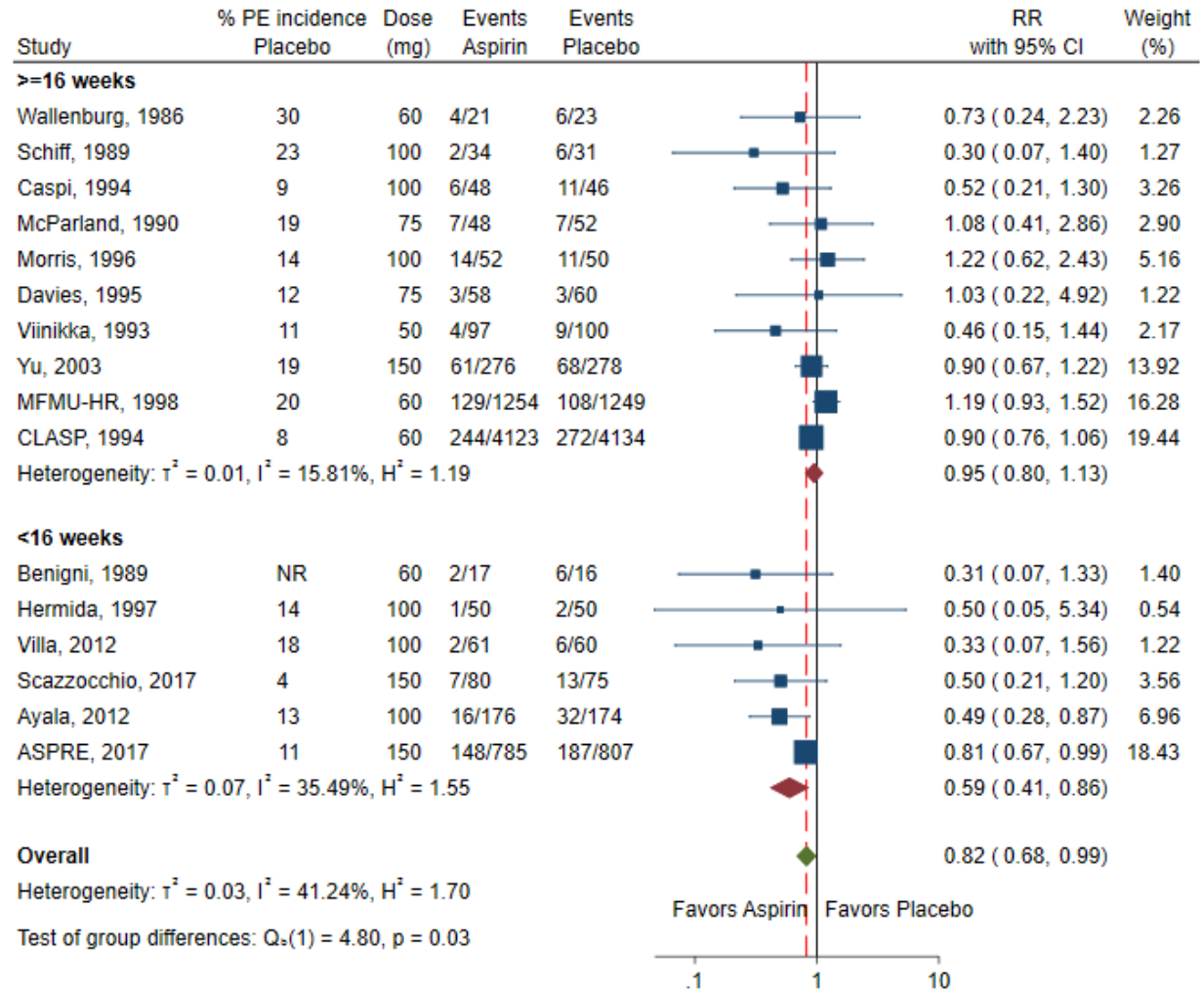
Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

Figure 4. Small for Gestational Age or Intrauterine Growth Restriction, Sorted by Study Size



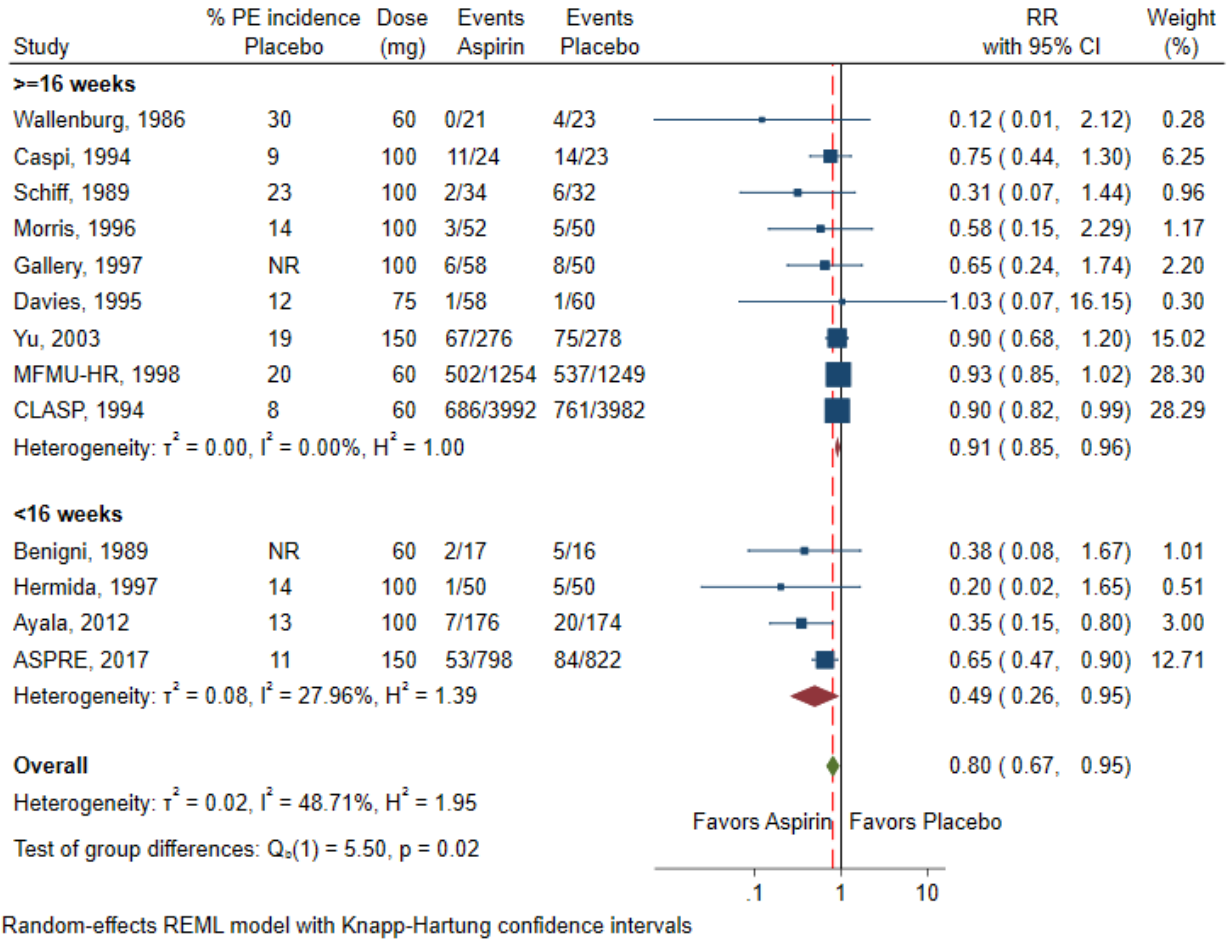
Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

Figure 5. Small for Gestational Age and Intrauterine Growth Restriction Stratified by Timing of Aspirin Initiation



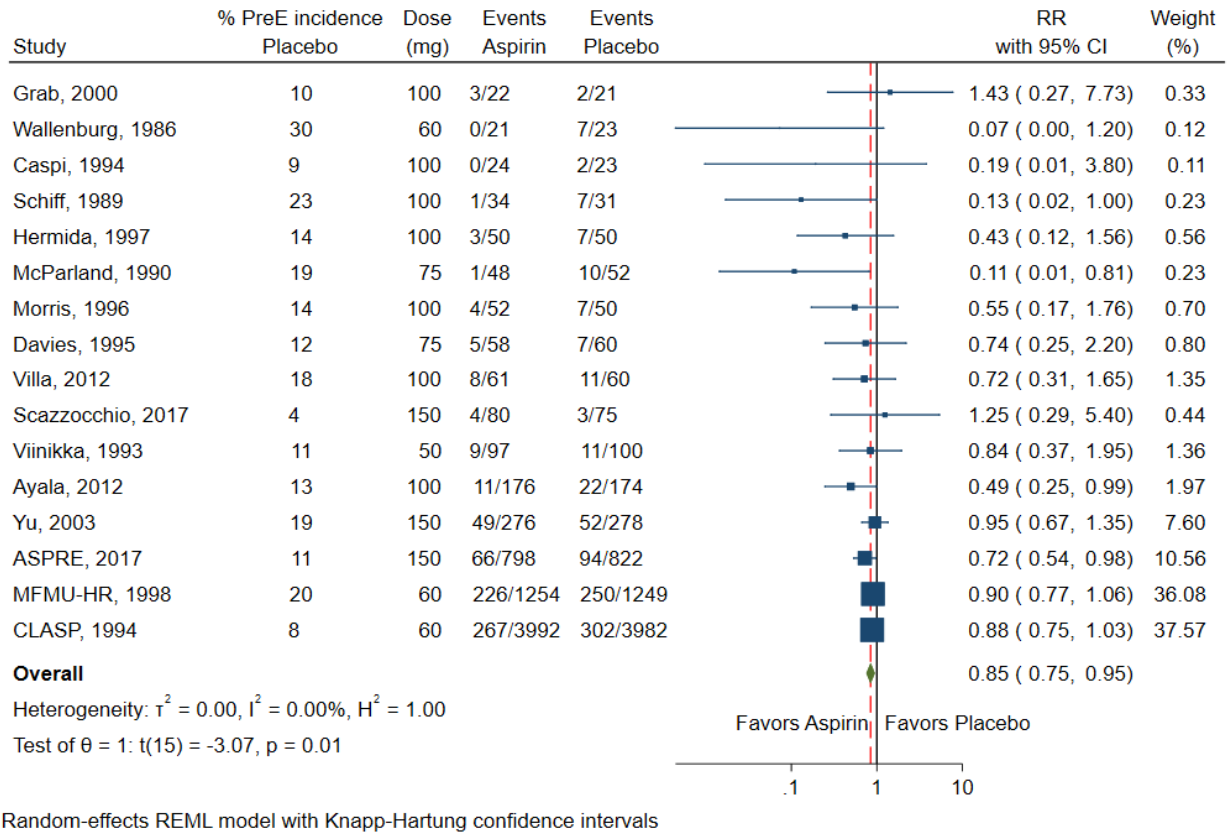
Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

Figure 6. Preterm Birth Stratified by Timing of Aspirin Initiation



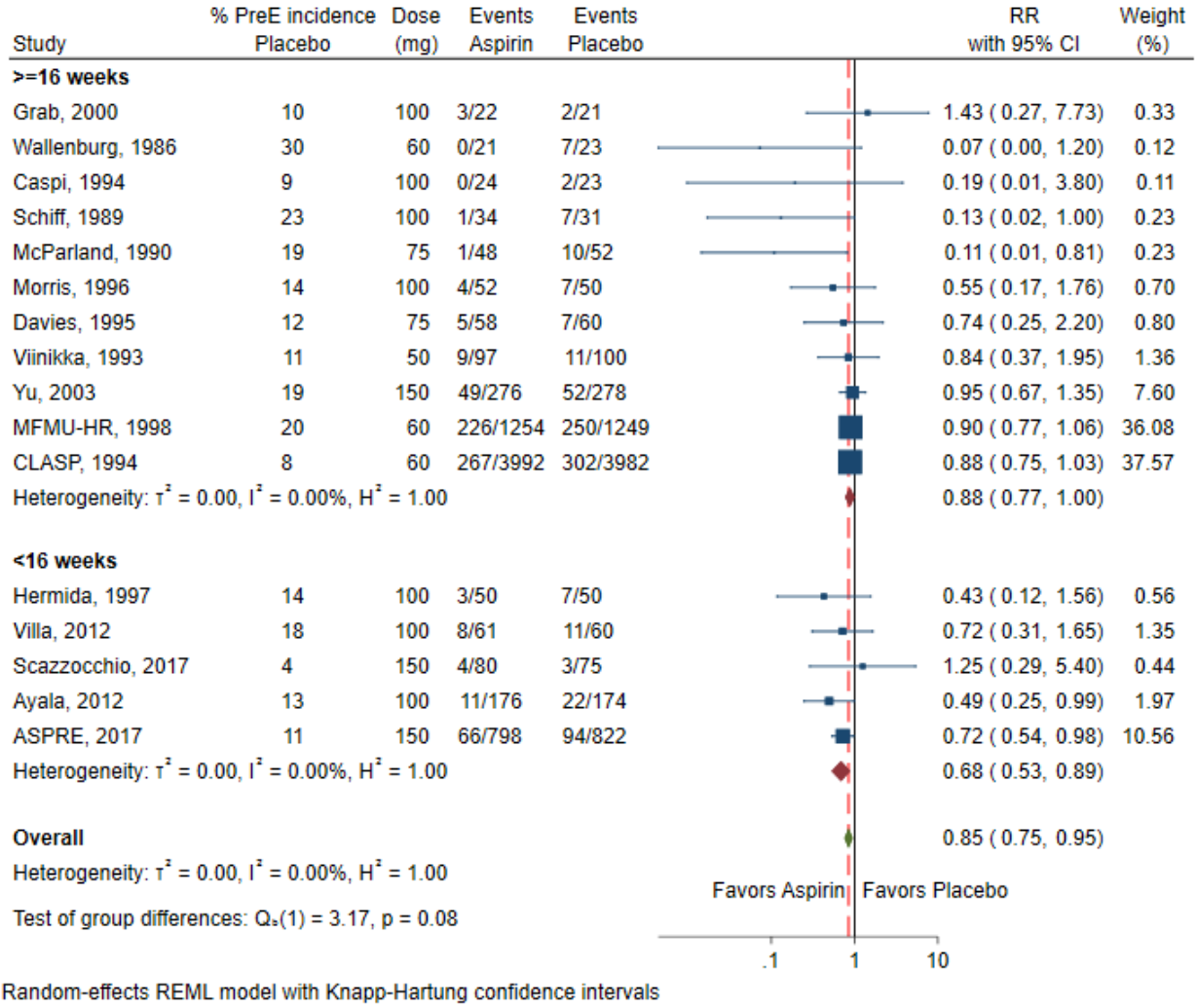
Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

Figure 7. Preeclampsia, Sorted by Study Size



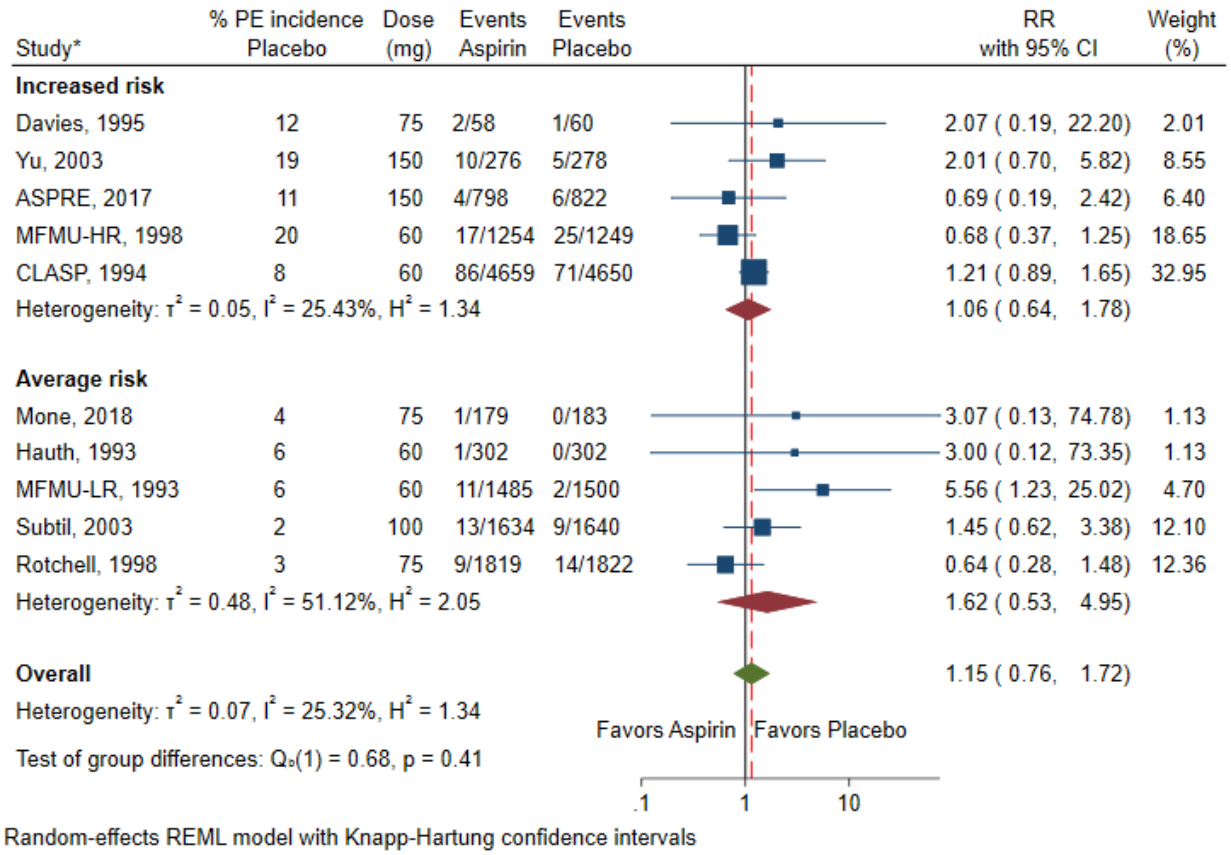
Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

Figure 8. Preeclampsia Stratified by Timing of Aspirin Initiation



Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

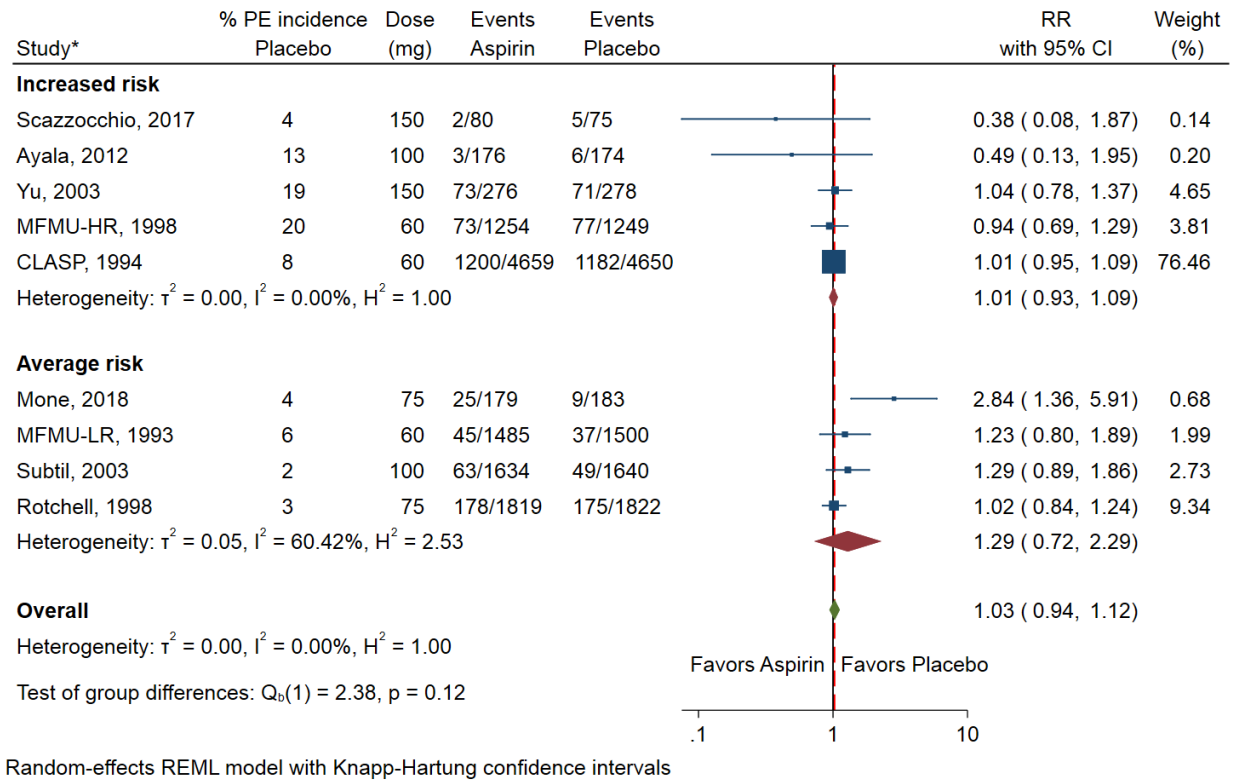
Figure 9. Placental Abruption Stratified by Risk, Sorted by Study Size



Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

*Excluded 3 studies with both arms having zero events.

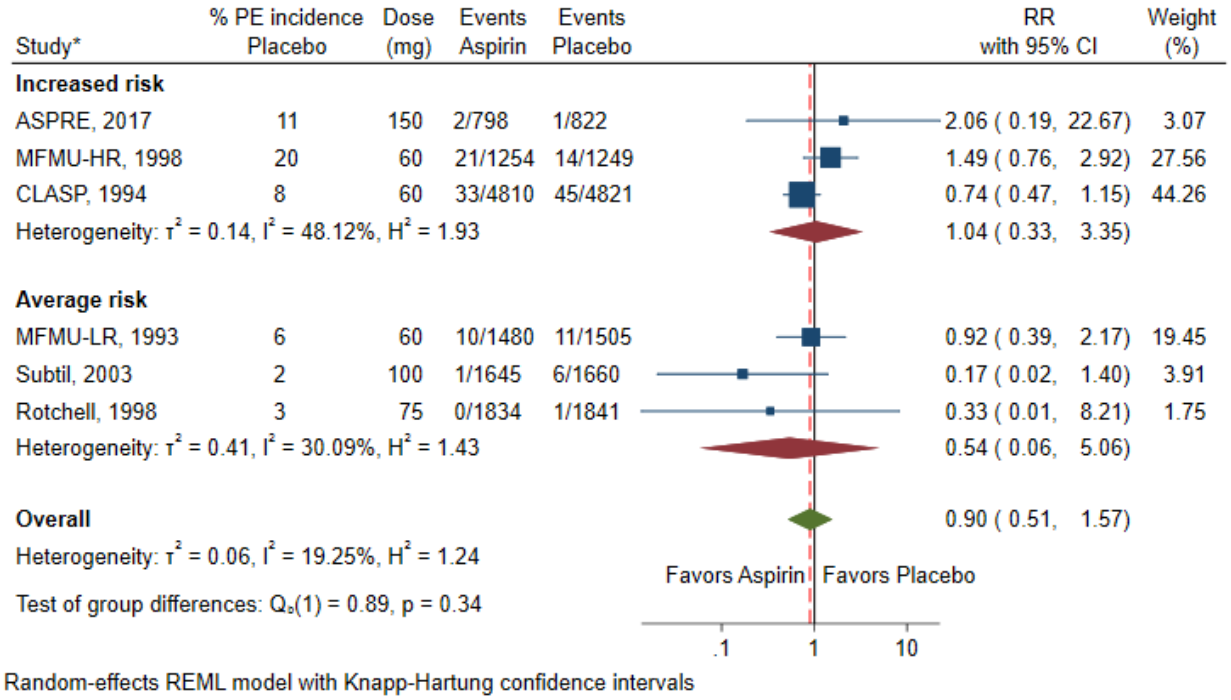
Figure 10. Postpartum Hemorrhage Stratified by Risk, Sorted by Study Size



Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

*Excluded 2 studies with both arms having zero events.

Figure 11. Fetal Intracranial Bleeding Stratified by Risk, Sorted by Study Size



Abbreviations: CI = Confidence interval; mg = Milligrams; PE = Preeclampsia; REML = Restricted maximum likelihood; RR = Risk ratio

*Excluded 3 studies with both arms having zero events.

Table 1. Existing Clinical Recommendations

Organization	Guideline	Definition of treatment population
National Institute for Health and Clinical Excellence (NICE)[183]	Advise pregnant women at **high risk** or with **more than 1 moderate risk factor** for pre-eclampsia to take 75–150 mg of aspirin daily from 12 weeks until the birth of the baby.	***High risk factors (any one)****:* Hypertensive disease during a previous pregnancy Chronic kidney disease Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome Type 1 or type 2 diabetes Chronic hypertension ***Moderate risk factors (>1 required)****:* First pregnancy Age 40 years or older Pregnancy interval of more than 10 years BMI of 35 kg/m^2 or more at first visit Family history of preeclampsia (mother, sister) Multi-fetal pregnancy
International Federation of Gynecology and Obstetrics (FIGO)[184]	Daily administration of aspirin starting at $\leq$ 16weeks and at a dose of $\geq$ 100 mg/d at night continuing until 36 weeks' gestation or presence of labor signs	Women with singleton pregnancy at gestational age 11-13^{6+} weeks based on risk assessment using a prediction algorithm using a combination of maternal factors with uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor at 11-13 weeks' gestation
American College of Obstetricians and Gynecologists (ACOG) [66]	Clinical risk assessment using patient medical history to identify patients for whom to recommend initiation of 81 mg/day of aspirin between 12 and 28 weeks of gestation (optimally before 16 weeks), continued until delivery Recommend low-dose aspirin if the patient has one or more high-risk factors. Consider low-dose aspirin if the patient has more than one moderate risk factor. Do not recommend low-dose aspirin for low-risk individuals (e.g., previous uncomplicated full-term delivery)	***High risk factors:*** History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome) ***Moderate risk factors (>1):*** Nulliparity Obesity (body mass index > 30) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age 35 years or older Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)
American Heart Association (AHA) and American Stroke Association (ASA)[68]	The AHA/ASA recommends that pregnant women with chronic primary or secondary hypertension or previous pregnancy-related hypertension should take low-dose aspirin from the 12th week of gestation until delivery to prevent preeclampsia.	Women with chronic primary or secondary hypertension or previous pregnancy-related hypertension
World Health Organization (WHO), 2011[65]	WHO recommends that women at high risk of preeclampsia take 75mg of aspirin daily, initiated before 20 weeks of pregnancy.	*High risk:* Previous preeclampsia Diabetes Chronic hypertension Renal disease Autoimmune disease Multiple pregnancy

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
ASPRE, 2017[59] Spain, Italy, UK, Israel, Belgium, Greece Good	1776	Increased risk, risk prediction algorithm at 11-13 weeks' gestation	Unconscious or severely ill status, learning difficulties or serious mental illness, major fetal abnormality, regular aspirin use within 28 days before screening, bleeding disorder, peptic ulceration, hypersensitivity to aspirin, long-term use of nonsteroidal antiinflammatory medication	150	Not specified 11 to 14 weeks; 36 weeks	Placebo	31.5*	IG: 68.5 CG: 66.1	White: 67.1 Black: 25.2 Asian: 6.4 Other: 1.3	IG: 7.1 CG: 7.2	IG: 6.1 CG: 7.4
Ayala, 2012[57] Spain Good	350	Increased risk, receiving pregnancy care at high-risk obstetric unit due to range of factors	Multiple pregnancy, chronic HTN or any other condition requiring the use of BP-lowering medication, cardiovascular disorders, chronic liver disease, any disease requiring the use of anti-inflammatory medication, DM or any other endocrine disease such as hyperthyroidism	100	Randomly assigned (various) 12 to 16 weeks; delivery	Placebo	30.7	IG: 49.4 CG: 55.1	NR	NR	NR

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
Benigni, 1989[88] Italy Fair	33	Increased risk, HTN or previous history of fetal death due to placental insufficiency, severe IUGR, early onset PreE [<32 weeks]	Women with antiphospholipid antibodies (lupus-like, anticoagulant, anticardiolipin antibodies)	60	Not specified 12 weeks; delivery	Placebo	31.5 (NR)	NR	NR	IG: 6.3 CG: 0	IG: 35.2 CG: 31.3
Caspi, 1994[94] Ireland Good	48	Increased risk, uncomplicated twin pregnancies	Chronic renal, cardiovascular, pulmonary or hepatic disorders, coagulopathy or peptic ulcer, gestational DM, known hypersensitivity to aspirin	100	Morning Start of the second trimester; delivery	Placebo	28.3	IG: 41.6 CG: 30.4	NR	NR	IG: 1.0 CG: 3.0

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
CLASP, 1994[95] US, Australia, Canada, Germany, Spain, Hong Kong, Ireland, Netherlands, New Zealand, Sweden, UK, Argentina, Belgium, Malaysia, Russia, UAE Good	9364	Increased risk, determined by clinician based on range of factors including obstetric history, family history, patient and pregnancy characteristics	Increased risk of bleeding, asthma, allergy to aspirin, or a high likelihood of immediate delivery	60	Not specified 12 to 32 weeks; delivery	Placebo	28.5	IG: 27.9 CG: 27.9	NR	IG: 20.7 CG: 20.1	IG: 19.9 CG: 20.2
Davies, 1995[96] UK Fair	122	Increased risk, hemoglobin concentration greater than 13.2 g/dL	Multiple pregnancy, DM, recurrent spontaneous abortions, or any contraindication to aspirin therapy	75	Not specified 18 weeks; delivery	Placebo	25.0	IG: 100 CG: 100	White: 95.8	IG: 10.3 CG: 13.3	IG: 0 CG: 0
Gallery, 1997[97] Australia Fair	108	Increased risk, chronic HTN or previous early, severe PreE	Women with history of aspirin allergy, aspirin-sensitive asthma, or preexisting bleeding diathesis	100	Not specified 17 to 19 weeks; two weeks before planned delivery	Placebo	28.5 (22-38)	IG: 42.0 CG: 43.0	White: 95.5	NR	IG: 57.0 CG: 52.0

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
Grab, 2000[101] Germany Fair	43	Increased risk, early IUGR, impaired uteroplacental blood, chronic HTN or previous still birth, growth restriction, or PreE	DM, proteinuric HTN; fetal malformations or chromosome abnormalities	100	Not specified 18 weeks; 38 weeks	Placebo	NR	NR	NR	NR	IG: 50.0 CG: 38.1
Hermida, 1997[98] Spain Good	100	Increased risk, receiving pregnancy care at high-risk hospital unit due to broad range of PreE factors	Multiple gestation pregnancy, chronic HTN, chronic liver disease, disease requiring the use of anti-inflammatory medication, DM, hyperthyroidism	100	Randomly assigned (various) 12 to 16 weeks; delivery	Placebo	30.2	NR	White: 100 Black: 0 Asian: 0 NatAm: 0 Hisp: 0 Other: 0	NR	NR
McParland, 1990[90] UK Fair	106	Increased risk, nulliparous with persistent abnormal Doppler flow-velocity waveforms at 24 weeks' gestation	Known aspirin allergy, maternal DM, bleeding disorders, peptic ulceration, systemic lupus erythematosus	75	Not specified 24 weeks; delivery	Placebo	26.1	IG: 100 CG: 100	White: 69.0 Black: 20.0 Asian: 7.0 Other: 4.0	IG: 16 CG: 23	NR

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
MFMU-HR, 1998[99] US Good	2539	Increased risk, four risk groups: DM, chronic HTN, multifetal gestation, previous PreE	Multifetal gestation in combination with DM, HTN,or proteinuria, history of PreE, current proteinuria	60	Not specified 13 to 26 weeks; delivery or if PreE developed	Placebo	26.5	NR	White: 32.7 Black: 56.3 Hisp: 10.8 Other: 0.5	IG: 16.8 CG: 16.4	NR
Morris, 1996[107]	102	Nulliparous with abnormal uterine artery waveforms at 18 weeks' gestation	Pregnancies dated at less than 17 weeks' or more than 19 weeks' of gestation	100	Not specified 17-19 weeks; NR	Placebo	23.8	100	NR	NR	NR
Scazzocchio, 2017[106] Spain Good	186	Increased risk, abnormal Doppler ultrasound at 11-14 weeks' gestation, maternal age > 18 years	Preexisting HTN, immune, renal, or cardiovascular disease, history of PreE in a previous pregnancy, history of gastric ulcer, known allergy or hypersensitivity to aspirin, hemorrhagic disease, fetal malformation, active treatment with heparin or aspirin before recruitment, multifetal gestation	150	Evening 11 to 14 weeks; delivery	Placebo	32.9	IG: 62.5 CG: 64.0	NR	IG: 11.3 CG: 12.0	IG: 0 CG: 0

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
Schiff, 1989[89] Israel Good	65	Increased risk, nulliparity, twin gestation, history of PreE, or positive rollover test	Chronic HTN, pregnancy induced hypertension or proteinuria in current pregnancy, long-term treatment with nonsteroidal anti-inflammatory drugs or use in previous 6 weeks, thrombocytopenia, coagulation disorders, heart failure, chronic renal or pulmonary disease, hepatic or peptic ulcer disease, hypersensitivity to aspirin	100	Not specified 28 or 29 weeks to 38 weeks	Placebo	27.4	NR	White: 100	NR	IG: 0 CG: 0
Viinikka, 1993[93] Finland Fair	208	Increased risk, HTN or previous severe PreE	None	50	Not specified 16 weeks; delivery	Placebo	33.0	IG: 25.2 CG: 23.8	NR	NR	IG: 86.4 CG: 91.4
Villa, 2012[104] Finland Fair	152	Increased risk, broad range of PreE risk factors and abnormal Doppler ultrasound at 12-14 weeks' gestation	Aspirin allergy, tobacco smoking in current pregnancy, multiple gestation pregnancy, asthma, peptic ulcer, placental ablation, inflammatory	100	Not specified 12 to 14 weeks; 35 weeks or delivery (whatever came first)	Placebo	30.9 (20-40)	IG: 26.2 CG: 15.0	NR	IG: 0 CG: 0	IG: 13.1 CG: 20.0

Table 2. Population, Study Design, and Intervention Characteristics, Increased Risk Population

Author, year Country Study quality	N rand	Included Populations	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
			bowel diseases, rheumatoid arthritis, hemophilia or thrombophilia								
Wallenburg, 1986[87] Netherlands Good	46	Increased risk, Angiotensin-II sensitivity determined by blood pressure test	HTN or cardiovascular renal disease	60	Morning 28 weeks; delivery	Placebo	24 (17-38)	IG: 100 CG: 100	NR	IG: 21.7 CG: 17.4	IG: 0 CG: 0
Yu, 2003[103] UK, Chile, South Africa, Brazil Good	560	Increased risk, abnormal Doppler ultrasound at 22-24 weeks' gestation	Chronic HTN, renal disease, cardiovascular disease, DM, bleeding disorders, systemic lupus erythematosus, peptic ulceration, hypersensitivity to aspirin, fetal abnormality or fetal growth restriction at 23 weeks' gestation	150	Not specified 22 to 24 weeks; 36 weeks	Placebo	29* (23-33)	IG: 26.8 CG: 23.4	White: 62.3 Black: 27.6 Other: 10.1	IG: 9.4 CG: 9.7	IG: 0 CG: 0

Abbreviations: ABPM = Ambulatory blood pressure monitoring; AIDS = Acquired immunodeficiency syndrome; CG = Control group; DM = Diabetes mellitus; Hisp = Hispanic; HTN = Hypertension; IG = Intervention group; NR = Not reported; PreE = Preeclampsia; UK = United Kingdom; US = United States

*Median

Table 3. Population, Study Design, and Intervention Characteristics, Average Risk Population

Author, year Country Study quality	N rand	Included Population	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
Hauth, 1993[91] US Good	606	Average risk, nulliparous	Any illness or condition known to increase the incidence of PreE or PIH (i.e. renal disease, collagen vascular disease, DM, multifetal gestation, chronic HTN)	60	Not specified No later than 22 weeks; delivery	Placebo	20.4	IG: 100 CG: 100	White: 28.5 Black: 71.5	NR	IG: 0 CG: 0
Mone, 2018[105] Ireland Fair	362	Average risk, nulliparous	Fetal congenital anomaly at recruitment, aspirin hypersensitivity	75	Evening 11 to 13 weeks; 36 weeks	No treatment	33.5 (19-44)	IG: 100 CG: 100	White: 96.8 Black: 0.8 Asian: 2.4 Other: 0	IG: 9.2 CG: 5.9	IG: 0 CG: 0
Rotchell, 1998[100] Barbados Good	3647	Average risk, nulliparous and multiparous	Increased risk of bleeding, known allergy or contraindication to aspirin, high likelihood of immediate delivery, previous placental abruption	75	Not specified 12 to 32 weeks; delivery	Placebo	NR	IG: 44.0 CG: 44.0	NR	NR	IG: 0.44 CG: 0.44
MFMU-LR, 1993[92] US Good	3135	Average risk, nulliparous	Chronic HTN, renal disease, DM, or other [unspecified] medical illnesses	60	Not specified 13 to 25 weeks; delivery	Placebo	20.5	IG: 100 CG: 100	White: 17.9 Black: 49.8 Hisp: 31.6	IG: 11.5 CG: 10.7	IG: 0 CG: 0

Table 3. Population, Study Design, and Intervention Characteristics, Average Risk Population

Author, year Country Study quality	N rand	Included Population	Main medical history exclusions	Aspirin dosage, mg	Treatment time of day, pregnancy duration	Control condition	Mean age (range)	Nulliparous, %	Race/ ethnicity, %	Smoking, %	Chronic HTN, %
Subtil, 2003[102] France, Belgium Good	3294	Average risk, nulliparous	Chronic HTN, antiphospholipid antibodies, lupus, contraindication to aspirin or other anticoagulant use (e.g., allergy, frequent hematomas or bleeding, hemorrhage during medical procedures, recent ulcer, severe asthma)	100	Not specified 14 to 20 weeks; 34 weeks	Placebo	24.7	IG: 100 CG: 100	NR	IG: 25.0 CG: 24.9	IG: 0 CG: 0

Abbreviations: CG = Control group; DM = Diabetes mellitus; Hisp = Hispanic; HTN = Hypertension; IG = Intervention group; NR = Not reported; PreE = Preeclampsia; PIH = Pregnancy-induced hypertension

Table 4. Patient Risk Factors and Clinical Tests Used to Identify Study Populations at Increased Risk for Preeclampsia

Author, Year	%Preeclampsia incidence in control group	Hx of preeclampsia or hypertension*	Maternal Age	Nulliparity	Multifetal gestation	Renal Disease	Metabolic disease	Hx of Stillbirth	Hx spontaneous abortion	Hx of SGA/IUGR	Diabetes	Prediction model†	Hemoglobin concentration	Positive rollover test	Angiotensin-II sensitivity	Abnormal Doppler readings
Benigni, 1989[88]	NR	x						x		x						
Gallery, 1997[97]	NR	x				x										
Scazzocchio, 2017‡[106]	4															x
CLASP, 1994[95]	8	x	x		x	x										
Caspi, 1994[94]	9				x											
Grab, 2000[101]	10	x						x		x						
ASPRE, 2017[59]	11	x										x				x
Viinikka, 1993[93]	11	x														
Davies, 1995[96]	12			x§									x			
Ayala, 2012[57]	13	x	x	x	x		x		x							
Hermida, 1997[98]	14	x	x	x	x		x		x							
Villa, 2012[104]	18	x							x	x	x					x
McParland, 1990[90]	19			x§												x
Yu, 2003‖[103]	19															x
MFMU-HR, 1998[99]	20	x			x						x					
Morris, 1996[107]	14			x												x
Schiff, 1989[89]	23	x		x	x									x		
Wallenburg, 1986[87]	30			x§											x	

Abbreviations: Hx = History; SGA/IUGR = Small for gestational age/intrauterine growth restriction; NR = Not reported

Table 4. Patient Risk Factors and Clinical Tests Used to Identify Study Populations at Increased Risk for Preeclampsia

[*] Includes personal history of gestational hypertension, chronic hypertension, or preeclampsia
[†] Prediction model includes maternal risk factors, serum biomarkers, Doppler ultrasound
[‡] Excluded individuals with a multifetal gestation or history of preeclampsia, hypertension, renal disease, or cardiovascular disease.
[§] Population limited to nulliparous individuals
[‖] Excluded criteria included individuals with history of hypertensive disease, renal and cardiovascular disease, and diabetes.

Table 5. Summary of Meta-Analysis Results

	No. studies reporting outcome (N Randomized)	Pooled Analysis No. studies (n analyzed)*	Pooled RR random effects model† (95% CI)	I^2 %	Tau^2	Effect Range	Effect Median (IQR)
Perinatal mortality	15 (15,527)	11 (13,860)	0.79 (0.66, 0.96)	0.0	0.0	0.31 to 5.15 ARD: -6.3 to 2.9	0.96 (0.59 to 1.10) ARD: 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 to 1.03 ARD: -19.5 to 0	0.65 (0.35 to 0.90) ARD: -5.7 (-12.9 to -3.0)
SGA/IUGR	16 (15,757)	16 (14,385)	0.82 (0.68, 0.99)	41.2	0.04	0.30 to 1.22 ARD: -25.7 to 4.9	0.63 (0.48 to 0.97) ARD: -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 to 1.43 ARD: -30.4 to 4.1	0.72 (0.31 to 0.89) ARD: -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 to 2.84 ARD: -4.2 to 9.1	1.02 (0.94 to 1.23) ARD: 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 to 5.56 ARD: -0.6 to 1.8	1.21 (0.96 to 2.07) ARD: 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 to 2.06 ARD: -0.3 to 0.6	0.94 (0.74 to 1.08) ARD: 0.0 (-0.1 to 0.0)

Abbreviations: ARD = Absolute risk difference; CI = Confidence interval; IQR = Interquartile range; k = Number of studies; N = Number of observations; RR = Risk ratio; SGA/IUGR = Small for gestational age / Intrauterine growth restriction

*Studies that reported no events in both study arms were excluded from the pooled analysis.
†Restricted maximum likelihood model with Knapp-Hartung confidence intervals

Table 6. Summary of Evidence

Key Question	No. of Studies (No. of observations) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1. Does aspirin reduce adverse maternal, perinatal, child, or combined health outcomes in pregnant persons at increased risk of preeclampsia? KQ1a. Does the effectiveness of aspirin for reducing adverse health outcomes vary by subpopulations defined by personal characteristics or preeclampsia risk factors?	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*** Reasonably **precise****	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 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 50-150mg a day

Table 6. Summary of Evidence

Key Question	No. of Studies (No. of observations) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ2. Does aspirin prevent preeclampsia in pregnant persons at increased risk for preeclampsia? KQ2a. Does the effectiveness of aspirin for reducing preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?	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 to placebo (pooled RR, 0.85 [95% CI, 0.75 to 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 effect sizes Confounding of study size with other study and participant characteristics could influence subgroup comparisons Subgroup effects limited by modest number 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 50-150mg a day

Table 6. Summary of Evidence

Key Question	No. of Studies (No. of observations) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ3. What are the harms of aspirin use to prevent preeclampsia during pregnancy? KQ3a. Do the harms of aspirin use to prevent preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?	21 RCTs (16 increased risk and 5 average risk populations) 14 good quality 7 fair quality (n = 26,757)	Studies conducted among average and increased risk populations did not find any clear evidence of harms associated with daily aspirin use (<150mg) 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%, k=11), or fetal intracranial bleeding (pooled RR, 0.90 [95% CI, 0.51, 1.57]; I^2 19%, k=9) were found. The result for placental abruption (pooled RR, 1.15 [95% CI, 0.76, 1.72] I^2 25%, k=13) was also null. Longer term followup from one large trial found no difference in child developmental outcomes for aspirin compared with 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.***	Studies in prenatal care settings in US or comparable settings, however mostly White participants Different criteria for identifying at risk populations Aspirin dose 50-150mg a day Harms from trials in average risk and increased risk populations

*Direction and magnitude of effects within and across for important perinatal health outcomes that could be quantitatively synthesized, with low to moderate statistical heterogeneity

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

*** Postpartum hemorrhage >1000 mL, longer term developmental harms, congenital malformations.

Table 7. Theoretical Number Needed to Treat (NNT) Across Different Levels of Outcome Incidence

Outcome	% Outcome incidence in population	Pooled RR estimate	% Absolute risk reduction	NNT (95% CI)
SGA/IUGR	7	0.82	-1	79 (45, 1429)
	17	0.82	-3	33 (18, 588)
	24	0.82	-4	23 (13, 417)
Preterm Birth	10	0.80	-2	50 (30, 200)
	17	0.80	-3	29 (18, 118)
	31	0.80	-6	16 (10, 65)
Perinatal mortality	1	0.79	-0.2	476 (294, 2500)
	6	0.79	-1	79 (49, 417)
Preeclampsia	9	0.85	-1	74 (44, 222)
	13	0.85	-2	51 (31, 154)
	19	0.85	-3	35 (21, 105)

Abbreviations: NNH = Number needed to harm; NNT= Number needed to treat; RR = Relative risk; SGA/IUGR = Small for gestational age/Intrauterine growth restriction

Table 8. Factors Associated With Increased Preeclampsia Risk Based on Patient Medical History*

Risk Level	Medical history and personal characteristics
High†	• History of preeclampsia • Chronic hypertension • Pregestational Type I or II diabetes mellitus • Multifetal gestation • Renal disease • Autoimmune disease (i.e., systemic lupus erythematous, antiphospholipid syndrome)
Moderate‡	• Nulliparous, having never given birth • Obesity (body mass index >30 kg/m^2) • Family history of preeclampsia (mother or sister) • Black race§ • Low socioeconomic status§ • Age ≥35 years • Personal pregnancy history (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval) • *In vitro* conception
Low	Previous uncomplicated full-term delivery

* Includes only risk factors that can be obtained from the patient medical history. Clinical measures such as serum biomarkers and uterine artery Doppler ultrasound have also been used in some trials to identify an increased risk population. A risk prediction algorithm combining clinical risk factors and biochemical and imaging markers was used in one trial for risk assessment in the first trimester among individuals with singleton pregnancies.

† Risk factors consistently and independently associated with the greatest risk of preeclampsia, with preeclampsia risk is at least twice as high as rates observed in an unselected population.

‡ Risk factors independently associated with moderate preeclampsia risk, some more consistently than others. Clinical judgment of risk for the specific patient and population or the presence of more than one risk factor could be used to identify a population at risk for preeclampsia at levels observed in the trial evidence on aspirin prophylaxis

§ Associated with increased risk due to environmental, social, and historical inequities shaping health exposures, access to health care, and the unequal distribution of resources, not biological propensities.

Appendix A. Detailed Methods

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword
lnk = subheading
de = index term
exp = explode
py = publication year

MEDLINE
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 22, 2019>
Search Strategy:
---

1 Pregnancy/
2 Pregnant Women/
3 pregnan$.ti,ab.
4 Pre-Eclampsia/
5 Hypertension, Pregnancy-Induced/
6 Eclampsia/
7 HELLP Syndrome/
8 preeclamp$.ti,ab.
9 eclamp$.ti,ab.
10 ((edema or oedema or proteinuria or hypertension or hypertensive) adj5 (gestosis or gestoses or antenatal or prenatal or gestation$ or perinatal)).ti,ab.
11 eph gestosis.ti,ab.
12 (tox?emi$ adj3 (eph or pregnan$)).ti,ab.
13 HELLP.ti,ab.
14 or/1-13
15 exp Aspirin/
16 Platelet Aggregation Inhibitors/
17 aspirin.ti,ab.
18 acetylsalicylic acid.ti,ab.
19 acetyl salicylic acid.ti,ab.
20 antiplatelet$.ti,ab.
21 anti platelet$.ti,ab.
22 (platelet$ adj3 (inhibit$ or antiaggregant$ or antagonist$)).ti,ab.
23 or/15-22
24 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt.
25 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/
26 Meta-Analysis as Topic/
27 control groups/ or double-blind method/ or single-blind method/
28 clinical trial$.ti,ab.

29 controlled trial$.ti,ab.
30 random$.ti,ab.
31 (metaanaly$ or meta analy$).ti,ab.
32 trial.ti.
33 placebo.ti,ab.
34 or/24-33
35 14 and 23 and 34
36 Pregnancy/
37 (pregnan$ or postpartum or post partum or antenatal or prenatal or gestation$ or perinatal or maternal or f?etal or f?etus or neonat$).ti,ab.
38 36 or 37
39 adverse effects.fs.
40 harm$.ti,ab.
41 adverse.ti,ab.
42 Hemorrhage/
43 h?emorrhag$.ti,ab.
44 bleed$.ti,ab.
45 blood loss.ti,ab.
46 exp Gastrointestinal Diseases/
47 (gastro$ or gastric or epigastric or instestinal).ti,ab.
48 (behavio* or development$).ti,ab.
49 or/39-48
50 38 and 49
51 Pregnancy complications/
52 Maternal death/
53 Maternal mortality/
54 Maternal Exposure/
55 Fetal death/
56 Fetal mortality/
57 Congenital abnormalities/
58 Postpartum hemorrhage/
59 Abruptio Placentae/
60 Abortion, Spontaneous/
61 Ductus Arteriosus, Patent/
62 Chorioamnionitis/
63 ((pregnan$ or maternal or f?etal or f?etus or neonat$) adj3 complication$).ti,ab.
64 ((congenital or birth or f?etal or f?etus) adj3 (defect$ or abnormal$ or anomal$ or malform$)).ti,ab.
65 ((maternal or f?etal or f?etus or perinatal) adj3 (death$ or mortality)).ti,ab.
66 miscarr$.ti,ab.
67 (spontaneous abortion$ or spontaneous labo?r).ti,ab.
68 abruptio$.ti,ab.
69 ductus arteriosus.ti,ab.
70 (chorioamnionitis or intraamniotic infection or intra-amniotic infection).ti,ab.
71 or/51-70
72 50 or 71
73 23 and 72
74 35 or 73
75 limit 74 to (english language and yr="2012 -Current")

76 75 not (animals/ not humans/)
77 remove duplicates from 76

PUBMED- [publisher supplied references only]
#1 Search pregnan*[tiab] OR preeclamp*[tiab] OR eclamp*[tiab]
#2 Search aspirin[tiab] OR acetylsalicylic acid[tiab] OR acetyl salicylic acid[tiab] OR antiplatelet$[tiab] OR anti platelet$[tiab] OR (platelet*[tiab] AND (inhibit*[tiab] OR antiaggregant*[tiab] OR antagonist*))
#3 Search (#1 AND #2)
#4 Search (#3 AND publisher[sb])
#5 Search (#3 AND publisher[sb]) Filters: Publication date from 2012/01/01
#6 Search (#3 AND publisher[sb]) Filters: Publication date from 2012/01/01; English

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)
#1 pregnan*:ti,ab,kw or preeclamp*:ti,ab,kw or eclamp*:ti,ab,kw
#2 ((edema:ti,ab or oedema:ti,ab or proteinuria:ti,ab or hypertension:ti,ab or hypertensive:ti,ab) NEAR/5 (gestosis:ti,ab or gestoses:ti,ab or antenatal:ti,ab or prenatal:ti,ab or gestation*:ti,ab or perinatal:ti,ab))
#3 eph gestosis:ti,ab
#4 (tox*emi*:ti,ab NEAR/3 (eph:ti,ab or pregnan*:ti,ab))
#5 #1 OR #2 OR #3 OR #4
#6 aspirin:ti,ab,kw or "acetylsalicylic acid":ti,ab,kw or antiplatelet*:ti,ab,kw or anti next platelet*:ti,ab,kw
#7 platelet*:ti,ab AND (inhibit*:ti,ab or antiaggregant*:ti,ab or antagonist*:ti,ab)
#8 #6 OR #7
#9 #5 AND #8 with Publication Year from 2012 to 2019, in Trials

Embase
No. Query Results
#1 'pregnancy'/de
#2 'pregnant woman'/de
#3 pregnan*:ab,ti
#4 'eclampsia and preeclampsia'/exp
#5 'pregnancy toxemia'/de
#6 'hellp syndrome'/de
#7 preeclamp*:ti,ab
#8 eclamp*:ti,ab
#9 ((edema OR oedema OR proteinuria OR hypertension OR hypertensive) NEAR/5 (gestosis OR gestoses OR antenatal OR prenatal OR gestation* OR perinatal)):ti,ab
#10 'eph gestosis':ti,ab
#11 (tox$emi* NEAR/3 (eph OR pregnan*)):ti,ab
#12 hellp:ti,ab
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 'acetylsalicylic acid'/de
#15 'antithrombocytic agent'/de
#16 aspirin:ti,ab
#17 'acetylsalicylic acid':ti,ab
#18 'acetyl salicylic acid':ti,ab

#19 antiplatelet*:ti,ab
#20 'anti platelet*':ti,ab
#21 (platelet* NEAR/3 (inhibit* OR antiaggregant* OR antagonist*)):ti,ab
#22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 'clinical trial'/de
#24 'controlled clinical trial'/de
#25 'randomized controlled trial'/exp
#26 'single blind procedure'/de
#27 'double blind procedure'/de
#28 'crossover procedure'/de
#29 'placebo'/de
#30 'randomized controlled trial (topic)'/de
#31 'clinical trial (topic)'/de
#32 'controlled clinical trial (topic)'/de
#33 'meta analysis'/exp
#34 'meta analysis (topic)'/de
#35 'clinical trial*':ti,ab
#36 'controlled trial*':ti,ab
#37 random*:ti,ab
#38 metaanaly*:ti,ab OR 'meta analy*':ti,ab
#39 trial:ti
#40 placebo:ti,ab
#41 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#42 #13 AND #22 AND #41
#43 pregnan*:ti,ab OR postpartum:ti,ab OR 'post partum':ti,ab OR antenatal:ti,ab OR prenatal:ti,ab OR gestation*:ti,ab OR perinatal:ti,ab OR maternal:ti,ab OR f$etal:ti,ab OR f$etus:ti,ab OR neonat*:ti,ab
#44 #1 OR #43
#45 'adverse drug reaction'/lnk OR 'complication'/lnk OR 'drug toxicity'/lnk OR 'side effect'/lnk
#46 harm*:ti,ab
#47 adverse:ti,ab
#48 'bleeding'/de
#49 h$emorrhag*:ti,ab
#50 bleed*:ti,ab
#51 blood AND loss:ti,ab
#52 'gastrointestinal disease'/de
#53 gastro*:ti,ab OR gastric:ti,ab OR epigastric:ti,ab OR instestinal:ti,ab
#54 behavio*:ti,ab OR development*:ti,ab
#55 #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54
#56 #44 AND #55
#57 'pregnancy disorder'/de
#58 'pregnancy complication'/de
#59 'maternal death'/de
#60 'maternal mortality'/de
#61 'maternal exposure'/de
#62 'fetus death'/de
#63 'fetus mortality'/de
#64 'congenital disorder'/de

#65 'postpartum hemorrhage'/de
#66 'solutio placentae'/de
#67 'spontaneous abortion'/de
#68 'patent ductus arteriosus'/de
#69 'chorioamnionitis'/exp
#70 ((pregnan* OR maternal OR f$etal OR f$etus OR neonat*) NEAR/3 complication*):ti,ab
#71 ((congenital OR birth OR f$etal OR f$etus) NEAR/3 (defect* OR abnormal* OR anomal* OR malform*)):ti,ab
#72 ((maternal OR f$etal OR f$etus OR perinatal) NEAR/3 (death* OR mortality)):ti,ab
#73 miscarr*:ti,ab
#74 'spontaneous abortion*':ti,ab OR 'spontaneous labo$r':ti,ab
#75 abruptio*:ti,ab OR 'solutio placentae':ti,ab
#76 'ductus arteriosus':ti,ab
#77 chorioamnionitis:ti,ab OR 'intraamniotic infection':ti,ab OR 'intra-amniotic infection':ti,ab
#78 #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77
#79 #56 OR #78
#80 #22 AND #79
#81 #42 OR #80
#82 (#42 OR #80) AND [english]/lim
#83 #82 AND (2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND [embase]/lim
#84 #83 NOT (('animal'/exp OR 'nonhuman'/de) NOT 'human'/exp)

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Populations	**KQs 1, 2 (Efficacy):** Pregnant persons at increased risk for preeclampsia based on: • Personal sociodemographic characteristics • Medical history • Diagnostic measurements or assays (e.g., uterine artery Doppler, biomarkers) • Risk prediction model **KQ 3 (Harms):** Pregnant persons, fetuses, infants, and children.	Nonhuman populations; nonpregnant persons; studies that only/exclusively include persons seeking fertility treatment; and other selected nongeneralizable populations
Disease/ condition	Primary prevention of preeclampsia	Trials of aspirin aimed at preventing other complications of pregnancy (e.g., stillbirth)
Setting	Countries categorized as "very high" on the 2017 Human Development Index (as defined by the United Nations Development Programme)	Countries not categorized as "very high" on the 2017 Human Development Index, as there is concern for nutritional deficiencies in developing countries
Interventions	Aspirin (≥50 mg)	Nonaspirin antiplatelet medications or aspirin combined with other potentially active interventions
Comparisons	Placebo or no treatment	Any active substance or intervention (e.g., nonaspirin medication, dietary supplements, dietary change, bed rest, or weight loss)

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Outcomes	**Maternal outcomes:** • Preeclampsia; Preecalmpsia with severe features • Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome • Eclampsia, puerperal cerebrovascular disorder, cerebrovascular hemorrhage, edema, or embolus • Renal or hepatic injury/failure • Pulmonary edema, adult respiratory distress syndrome • Disseminated intravascular coagulation • Mental health diagnoses or symptoms • Maternal mortality • Measures of well-being or quality of life **Potential treatment harms:** • Abruptio placentae • Postpartum hemorrhage • Gastrointestinal complications (e.g., bleeding ulcer) **Fetal/neonatal/child outcomes:** • Preterm birth (<37 weeks): late preterm birth (34-36 weeks), moderate perterm birth, (32-34 weeks), very preterm birth (<32 weeks), extremely preterm birth (<28 weeks) • Mean gestational age • Low birth weight • Intrauterine growth restriction/small for gestational age (<10th percentile weight for gestational age) • Stillbirth or neonatal mortality **Potential treatment harms:** • Intracranial fetal bleeding • Fetal malformations • Nonclosure of the ductus arteriosus • Chorioamnionitis • Child behavioral or developmental problems	• Length of hospital stay (without indication) • Intensive care unit admission • Neonatal intensive care unit admission
Study Designs	**KQs 1, 2 (Efficacy):** Randomized, controlled trial, individual participant data meta-analysis of trials **KQ 3 (Harms):** Randomized, controlled trial or comparative cohort studies, individual participant data meta-analysis of trials	**KQs 1, 2 (Efficacy):** Any nonrandomized controlled trial **KQ 3 (Harms):** Editorials, narrative review, commentary, postmarketing surveillance, or case reports
Study Quality	Good- and fair-quality studies	Poor-quality studies
Language	English	Languages other than English

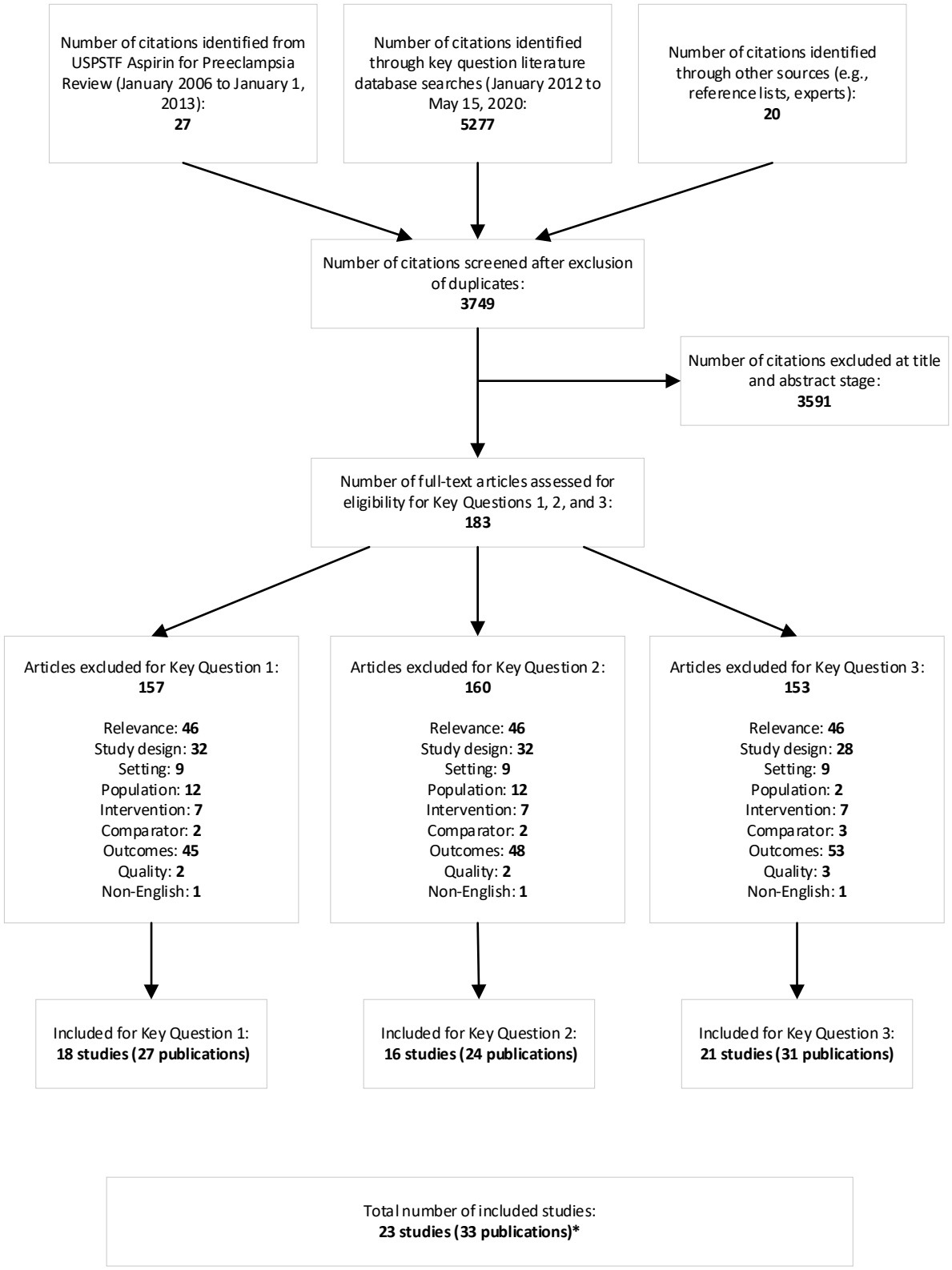
Abbreviations: KQ = Key Question; USPSTF = U.S. Preventative Services Task Force

Appendix A Table 2. Study Design-Specific Quality Rating Criteria

Study Design	Adapted Quality Criteria
Randomized and non-randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[74]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer

Appendix B Figure 1. Literature Flow Diagram



*Studies may appear in more than one Key Question

Below is a list of included studies and their ancillary publications (indented below main results publication):

Ayala, DE, Ucieda, R, et al. Chronotherapy With Low-Dose Aspirin for Prevention of Complications in Pregnancy. Chronobiol.Int. 30(1-2): 260-279. 2012. https://dx.doi.org/10.3109/07420528.2012.717455.

Benigni, A, Gregorini, G, 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. 321(6): 357-362. 1989. https://dx.doi.org/

MFMU-HR, Caritis, Steve, Sibai, Baha, et al. Low-Dose Aspirin to Prevent Preeclampsia in Women at High Risk. N Engl J Med. 338(11): 701-705. 1998. https://dx.doi.org/10.1056/NEJM199803123381101

Abramovici, A, Jauk, V, et al. Low-dose aspirin, smoking status, and the risk of spontaneous preterm birth. Am J Perinatol. 32(5): 445-50. 2015. PMID: 25261702. https://dx.doi.org/10.1055/s-0034-1390352

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Appendix C. Included Studies

Reason for Exclusion*
E1. Relevance **E1a.** Not primary data (e.g., editorial, narrative review)
E2. Study design **E2a.** Single arm cohort, case-control study
E3. Setting **E3a.** Study country not a "very high" HDI
E4. Population **E4a.** Population not at increased risk (e.g. nulliparous otherwise healthy women)
E5. Intervention **E5a.** Aspirin plus other medication **E5b.** Intervention other than aspirin
E6. Comparator **E6a.** Comparative effectiveness – active comparator
E7. No relevant outcomes **E7a.** Secondary analysis of included study with no relevant outcomes **E7b.** Preliminary reporting, incomplete information
E8. Poor study quality
E9. Non-English language

*Assigned at full-text phase

1. Abramovici, A, Jauk, V, et al. Analysis of low-dose aspirin by smoking status for select perinatal outcomes. Am J Obstet Gynecol. 208(1): S261. 2013. https://dx.doi.org/10.1016/j.ajog.2012.10.779 **KQ1E7b, KQ2E7b, KQ3E7b**

2. Abramovici, A, Jauk, V, et al. Low-dose aspirin is associated with a reduction in spontaneous preterm birth among non-smokers. Am J Obstet Gynecol. 208(1): S260-S261. 2013. https://dx.doi.org/10.1016/j.ajog.2012.10.778 **KQ1E7b, KQ2E7b, KQ3E7b**

3. Adkins, K, Allshouse, A, et al. Impact of low-dose aspirin on fetal growth in diabetic pregnancies: the importance of white classification. Am J Obstet Gynecol. 216(1): S292-S293. 2017. **KQ1E7b, KQ2E7b, KQ3E7b**

4. Allshouse, AA, Jessel, RH, et al. The impact of low-dose aspirin on preterm birth: secondary analysis of a randomized controlled trial. J Perinatol. 36(6): 427-31. 2016. PMID: 26890552. https://dx.doi.org/10.1038/jp.2016.3 **KQ1E2, KQ2E2, KQ3E2**

5. Ananth, C, Coletta-Lucas, J, et al. Timing of adverse neonatal outcomes in pregnancies complicated by preeclampsia and small for gestational age births in a cohort of high-risk pregnancies. Am J Obstet Gynecol. 208(1): S264. 2013. https://dx.doi.org/10.1016/j.ajog.2012.10.786 **KQ1E7b, KQ2E7b, KQ3E7b**

6. Anca-Daniela, S, Banica, R, et al. Low dose aspirin for preventing fetal growth restriction: A randomised trial. J Perinat Med. 43. 2015. https://dx.doi.org/10.1515/jpm-2015-2002 **KQ1E7b, KQ2E7b, KQ3E7b**

7. Anderson, S, Jauk, V, et al. Mid-trimester blood pressures below 140/90 and risk of small-for-gestational age (SGA) in pregnancies complicated by chronic hypertension. Am J Obstet Gynecol. 212(1): S345-S346. 2015. https://dx.doi.org/10.1016/j.ajog.2014.10.914 **KQ1E7b, KQ2E7b, KQ3E7b**

8. Andrikopoulou, M, Purisch, SE, et al. Beyond preeclampsia: Low dose aspirin reduces spontaneous preterm birth. Am J Obstet Gynecol. 218(1): S10. 2018. **KQ1E4a, KQ2E4a, KQ3E7a**

9. Andrikopoulou, M, Purisch, SE, et al. Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women. Am J Obstet Gynecol. 219(4): 399.e1-399.e6. 2018. PMID: 29913174. https://dx.doi.org/10.1016/j.ajog.2018.06.011 **KQ1E4a, KQ2E4a, KQ3E7a**

10. Ankumah, NA, Cantu, J, et al. Risk of adverse pregnancy outcomes in women with mild chronic hypertension before 20 weeks of gestation. Obstet Gynecol. 123(5): 966-72. 2014. PMID: 24785847. https://dx.doi.org/10.1097/AOG.0000000000000205 **KQ1E2, KQ2E2, KQ3E2**

11. Ankumah, NA, Tita, A, et al. Pregnancy outcome vary by blood pressure level in women with mild-range chronic hypertension. Am J Obstet Gynecol. 208(1): S261-S262. 2013. https://dx.doi.org/10.1016/j.ajog.2012.10.780 **KQ1E7b, KQ2E7b, KQ3E7b**

12. Askie, L, Duley, L. Associations between the timing and dosing of aspirin prophylaxis and term and preterm pre-eclampsia. BMJ Evid Based Med. 2018. PMID: 29880699. https://dx.doi.org/10.1136/bmjebm-2018-110931 **KQ1E1a, KQ2E1a, KQ3E1a**

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16. Baschat, AA, Dewberry, D, et al. Maternal blood-pressure trends throughout pregnancy and development of pre-eclampsia in women receiving first-trimester aspirin prophylaxis. Ultrasound Obstet Gynecol. 52(6): 728-733. 2018. PMID: 29266502. https://dx.doi.org/10.1002/uog.18992 **KQ1E2a, KQ2E2a, KQ3E2a**

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19. Cantu, J, Biggio, J, et al. Timing of initiation of low-dose aspirin therapy and preeclampsia prevention in high-risk women. Am J Obstet Gynecol. 208(1): S266. 2013. https://dx.doi.org/10.1016/j.ajog.2012.10.793 **KQ1E7b, KQ2E7b, KQ3E7b**

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50. 178-178. 2017. https://dx.doi.org/10.1002/UOG.18072 **KQ1E7b, KQ2E7b, KQ3E7b**

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33. Dixon, CL, Marrs, C, et al. Effect of Low-Dose Aspirin on the Time of Onset of Preeclampsia and Time of Delivery. Am J Perinatol. 34(12): 1219-1226. 2017. PMID: 28445915. https://dx.doi.org/10.1055/s-0037-1602421 **KQ1E7a, KQ2E7a, KQ3E7a**

34. El-Achi, V, Park, F, et al. Does low dose aspirin prescribed for risk of early onset

preeclampsia reduce the prevalence of preterm prelabor rupture of membranes?. J Matern Fetal Neonatal Med. 1-6. 2019. PMID: 31018725. https://dx.doi.org/10.1080/14767058.2019.1611768 **KQ1E2, KQ2E2, KQ3E8**

35. Erratum: Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history (American Journal of Obstetrics and Gynecology (2017) 217(5) (585.e1–585.e5) (S0002937817309298) (10.1016/j.ajog.2017.07.038)). Am J Obstet Gynecol. 218(4): 454. 2018. https://dx.doi.org/10.1016/j.ajog.2018.01.002 **KQ1E1a, KQ2E1a, KQ3E1a**

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43. Greene, MF, Solomon, CG. Aspirin to prevent preeclampsia. N Engl J Med. 377(7): 690-691. 2017. https://dx.doi.org/10.1056/NEJMe1708920 **KQ1E1a, KQ2E1a, KQ3E1a**

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45. Gyamfi-Bannerman, C, Fratto, V, et al. Late preterm neonatal morbidity in high-risk hypertensive versus normotensive women. Am J Obstet Gynecol. 208(1): S207. 2013. https://dx.doi.org/10.1016/j.ajog.2012.10.645 **KQ1E7b, KQ2E7b, KQ3E7b**

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51. Hastie, R, Hesselman, S, et al. Prophylactic aspirin use during pregnancy is associated antenatal complications; a Swedish population register-based cohort study. Pregnancy Hypertens. 17. S16. 2019. **KQ1E2, KQ2E2, KQ3E2**a

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https://dx.doi.org/10.1007/s11906-016-0664-3 **KQ1E2, KQ2E2, KQ3E2**

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Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
ASPRE, 2017[59] Good	Aged 18 years or more, singleton pregnancy, live fetus at the time that scanning was performed at 11 to 13 weeks' gestation, high risk (>1 in 100) for preterm preeclampsia according to the screening algorithm	Unconscious or severely ill status, learning difficulties or serious mental illness, major fetal abnormality identified at the time that scanning was performed at 11 to 13 weeks of gestation, regular treatment with aspirin within 28 days before screening, bleeding disorder such as von Willebrand's disease, peptic ulceration, hypersensitivity to aspirin, long-term use of nonsteroidal anti-inflammatory medication, and participation in another drug trial within 28 days before screening	31.5*	White: 67.1 Black: 25.2 Asian: 6.4 Other: 1.3	IG: 26.7 CG: 26.5	IG: 68.5 CG: 66.1	IG: 7.1 CG: 7.2	Previous PreE IG: 10.9 CG: 10.2 Chronic HTN IG: 6.1 CG: 7.4 Chronic DM IG: 1.9 CG: 1.2
Ayala, 2012[57] Good	Higher risk for gestational HTN or preeclampsia, receiving medical care and follow-up at the Obstetric Physiopathology service (high-risk unit) of the hospital, ≤16 weeks' gestation, maternal age ≥18 years	Multiple pregnancy, chronic HTN or any other condition requiring the use of BP-lowering medication, cardiovascular disorders (unstable angina pectoris, heart failure, life-threatening arrhythmia, atrial fibrillation, kidney failure, and grade III–IV retinopathy), chronic liver disease, any disease requiring the use of anti-inflammatory medication, DM or any other endocrine disease such	30.7	NR	IG: 25.4 CG: 25.5	IG: 49.4 CG: 55.1	NR	NR

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
		as hyperthyroidism, history of drug/alcohol abuse, night/ shiftwork employment, AIDS, intolerance to ABPM, and inability to communicate and comply with all of the study requirements						
Benigni, 1989[88] Fair	At high risk of pregnancy-induced HTN, with HTN, or previous obstetrical history (fetal death due to placental insufficiency, severe IUGR, early onset PreE [<32 weeks])	Women with antiphospholipid antibodies (lupus-like, anticoagulant, anticardiolipin antibodies)	31.5	NR	NR	NR	IG: 6.3 CG: 0	Previous PreE IG: 50 CG: 35 Chronic HTN IG: 35.2 CG: 31.3
Caspi, 1994[94] Good	Uncomplicated twin pregnancies	Chronic renal, cardiovascular, pulmonary or hepatic disorders, pastor present coagulopathy or peptic ulcer, gestational DM and known hypersensitivity to aspirin	28.3	NR	NR	IG: 41.6 CG: 30.4	NR	Chronic HTN IG: 1.0 CG: 3.0 Multifetal Gestation IG: 100 CG: 100
CLASP, 1994[95] Good	12 to 32 weeks' gestation, at sufficient risk of developing preeclampsia or IUGR for the use of low-dose aspirin to be considered; risk factors for prophylactic aspirin use defined as history of preeclampsia or IUGR in previous pregnancy, chronic	Increased risk of bleeding, asthma, allergy to aspirin, or a high likelihood of immediate delivery	28.5	NR	NR	IG: 27.9 CG: 27.9	IG: 20.7 CG: 20.1	Chronic HTN IG: 19.9 CG: 20.2 Chronic DM IG: 2.7 CG: 3.1

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
	HTN, renal disease, maternal age, family history, or multiple pregnancy; or, for therapeutic use, women with signs or symptoms of preeclampsia or IUGR in current pregnancy							
Davies, 1995[96] Fair	No previous pregnancy beyond 12 weeks' gestation, 12 to 19 weeks' gestation, hemoglobin concentrate > 13.2 g/dL, DBP <90 mmHg, no proteinuria at time of randomization	Multiple pregnancy, DM, recurrent spontaneous abortions, or any contraindication to aspirin therapy	25.0	White: 95.8	NR	IG: 100 CG: 100	IG: 10.3 CG: 13.3	Previous PreE IG: 0 CG: 0 Chronic HTN IG: 0 CG: 0 Chronic DM IG: 0 CG: 0 Multifetal Gestation IG: 0 CG: 0
Gallery, 1997[97] Fair	<16 weeks' gestation, at high risk of developing preeclampsia	Women with a history of aspirin allergy, aspirin-sensitive asthma, or preexisting bleeding diathesis	28.5 (22-38)	White: 95.5	NR	IG: 42.0 CG: 43.0	NR	Previous PreE IG: 17.0 CG: 22.0 Chronic HTN IG: 57.0 CG: 52.0
Grab, 2000[101] Fair	Singleton pregnancies, <20 weeks' gestation with early IUGR,	DM, preexisting proteinuric HTN, fetal malformations, or	NR	NR	NR	NR	NR	Previous PreE IG: 40.9

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
	impaired uteroplacental blood, chronic HTN, history of still birth, growth restriction, or preeclampsia	chromosome abnormalities						CG: 42.9 Chronic HTN IG: 50.0 CG: 38.1 Multifetal Gestation IG: 0 CG: 0
Hauth, 1993[91] Good	Nulliparous, age 28 years or younger, no later than 22 weeks of gestation	History of illness or conditions known to increase the incidence of PreE or PIH (i.e. renal disease, collagen vascular disease, DM, multifetal gestation, chronic HTN), failed "run-in" test for compliance	20.4	White: 28.5 Black: 71.5	NR	IG: 100 CG: 100	NR	Chronic HTN IG: 0 CG: 0 Chronic DM IG: 0 CG: 0
Hermida, 1997[98] Good	Absence of any condition requiring the use of antihypertensive medication, maternal age 18 to 40 years, <16 weeks' gestation.	Multiple pregnancy, chronic HTN, chronic liver disease, any disease requiring the use of anti-inflammatory medication, DM, or any other endocrine disease such as hyperthyroidism, intolerance to the use of ambulatory BP monitor, among others	30.2	White: 100	IG: 25.3 CG: 24.9	NR	NR	Multifetal Gestation IG: 0 CG: 0
McParland, 1990[90] Fair	Nulliparous, persistent abnormal Doppler flow-velocity waveforms	Known ASA allergy, maternal DM, bleeding disorders, peptic ulceration, systemic lupus erythematosus	26.1	White: 69.0 Black: 20.0 Asian: 7.0 Other: 4.0	IG: 24.1 CG: 24.6	IG: 100 CG: 100	IG: 16 CG: 23	NR

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
MFMU-HR, 1998[99] Good	One of four high risk groups: DM, chronic HTN, multifetal gestation, or previous preeclampsia	Multifetal gestation in combination with DM, HTN, or proteinuria, history of PreE, current proteinuria	26.5	White: 32.7 Black: 56.3 Hisp: 10.8 Other: 0.5	NR	NR	IG: 16.8 CG: 16.4	NR
Mone, 2018[105] Fair	Nulliparous, aged 18 years or older, 11 to 13 weeks' gestation, viable singleton pregnancy, did not meet criteria for taking aspirin based upon major preeclampsia risk factors (chronic kidney disease, autoimmune disease, DM, and chronic HTN)	Participants already taking part in a clinical trial, coexistence of a fetal congenital anomaly at recruitment, aspirin hypersensitivity	33.5 (19-44)	White: 96.8 Black: 0.8 Asian: 2.4	IG: 25.2 CG: 22.9	IG: 100 CG: 100	IG: 9.2 CG: 5.9	Chronic HTN IG: 0 CG: 0 Chronic DM IG: 0 CG: 0
Morris, 1996[107]	Nulliparous with abnormal uterine artery waveforms at 18 weeks' gestation	Pregnancies dated at less than 17 weeks' or more than 19 weeks' of gestation	23.8	NR	NR	IG: 100 CG: 100	NR	NR
Rotchell, 1998[100] Good	12 to 32 weeks' gestation without contraindications	Increased risk of bleeding, known allergy to aspirin, high likelihood of immediate delivery or previous placental abruption	NR	NR	NR	IG: 44.0 CG: 44.0	NR	Chronic HTN IG: 0.44 CG: 0.44 Chronic DM IG: 0.71 CG: 0.44 Gestational DM IG: NR

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
								CG: NR Multifetal Gestation IG: 0.82 CG: 1.0
Scazzocchio, 2017[106] Good	Aged 18 years or older, singleton pregnancy, 11 to 14 weeks' gestation, crown-rump length of 45 to 84 mm, mean UtA pulsatility index > 95th percentile	Preexisting HTN, immune, renal, or cardiovascular disease, history of preeclampsia in a previous pregnancy, history of gastric ulcer, known allergy or hypersensitivity to aspirin, hemorrhagic disease, fetal malformation (including chromosomopathy), active treatment with heparin or aspirin before recruitment, multifetal gestation, maternal age <18 years	32.9	NR	IG: 23.5 CG: 23.5	IG: 62.5 CG: 64.0	IG: 11.3 CG: 12.0	Previous PreE IG: 0 CG: 0 Chronic HTN IG: 0 CG: 0

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
Schiff, 1989[89] Good	At least one of the following risk factors: nulliparity, twin gestation, history of PreE; had to screen positive during a roll-over test (which tested BP before & after rolling from the left side to back)	History of chronic HTN, long-term treatment with nonsteroidal anti-inflammatory drugs or the use of these drugs in the previous 6 weeks, PIH detected prior to screening, proteinuria detected before screening, history of thrombocytopenia, coagulation disorders, heart failure, chronic renal or pulmonary disease, hepatic or peptic ulcer disease, history of hypersensitivity to ASA	27.4	White: 100	NR	NR	NR	Previous PreE IG: 17.6 CG: 16.1 Chronic HTN IG: 0 CG: 0 Multifetal Gestation IG: 8.8 CG: 6.5
MFMU-LR, 1993[92] Good	Nulliparous, 13 to 25 weeks' gestation, BP <135/85 mmHg, no proteinuria	History of chronic HTN, renal disease, DM, or other medical illnesses	20.5	White: 17.9 Black: 49.8 Hisp: 31.6	NR	IG: 100 CG: 100	IG: 11.5 CG: 10.7	Chronic HTN IG: 0 CG: 0 Chronic DM IG: 0 CG: 0 Multifetal Gestation IG: 1.3 CG: 1.2

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
Subtil, 2003[102] Good	Nulliparous (no previous delivery at or after 22 weeks' gestation), 14 to 20 weeks' gestation, planned to continue prenatal care and give birth in the participating facility, provided written informed consent	History of HTN, potential indication (antiphospholipid antibodies, lupus) for or a contraindication (allergy, frequent hematomas or bleeding, history of hemorrhage during surgery, tooth extraction or other, recent gastric or duodenal ulcer, severe asthma) to aspirin or other anticoagulant treatment during this pregnancy	24.7	NR	IG: 22.5 CG: 22.3	IG: 100 CG: 100	IG: 25.0 CG: 24.9	Chronic HTN IG: 0 CG: 0 Multifetal Gestation IG: 1.2 CG: 1.6
Viinikka, 1993[93] Fair	At risk of developing preeclampsia, defined as having arterial HTN (BP without treatment >140/90 mmHG already before pregnancy), or having severe preeclampsia in a previous pregnancy	None	33.0	NR	NR	IG: 25.2 CG: 23.8	NR	Previous PreE IG: 13.6 CG: 8.6 Chronic HTN IG: 86.4 CG: 91.4
Villa, 2012[104] Fair	Presenting with at least one of the following risk factors: <20 years of age, >40 years of age, BMI >30, chronic HTN (> or equal to 140/90 mmHg or medication for HTN before 20 weeks' gestation), Sjorgren's syndrome, lupus, or history of one of the following: gestational DM, PreE, SGA, fetus	Allergy to aspirin, tobacco smoking during this pregnancy, multiple pregnancy, history of one or more of the following: asthma, peptic ulcer, placental ablation, inflammatory bowel diseases, rheumatoid arthritis, hemophilia or thrombophilia	30.9 (20-40)	NR	IG: 27.9 CG: 29.7	IG: 26.2 CG: 15.0	IG: 0 CG: 0	Previous PreE IG: 32.8 CG: 28.3 Chronic HTN IG: 13.1 CG: 20.0 Gestational DM IG: 6.6 CG: 16.7

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
	mortus (fetal death after 22 weeks' gestation or >500 g weight in a previous pregnancy), and transvaginal color doppler ultrasound at all patients from 12 +0 weeks to 13 +6 weeks' gestation, second degree diastolic notch present eligible for randomization							
Wallenburg, 1986[87] Good	Healthy, nulliparous, uncomplicated pregnancy of 26 weeks' duration, maximum diastolic blood pressure of 80mmHg, positive angiotensin II sensitivity test	History of HTN or cardiovascular renal disease	24 (17-38)	NR	NR	IG: 100 CG: 100	IG: 21.7 CG: 17.4	Previous PreE IG: 0 CG: 0 Chronic HTN IG: 0 CG: 0 Gestational HTN IG: 0 CG: 0
Yu, 2003[103] Good	Mean PI above 1.6, early diastolic notching of uterine arteries identified by transvaginal color Doppler ultrasound	Pre-existing HTN, renal, or cardiovascular disease, DM, bleeding disorders, systemic lupus erythematosus, peptic ulceration, hypersensitivity to aspirin, and the finding at the 23-week scan of a fetal abnormality or fetal growth restriction	29* (23-33)	White: 62.3 Black: 27.6 Other: 10.1	IG: 25.0 CG: 25.6	IG: 26.8 CG: 23.4	IG: 9.4 CG: 9.7	Previous PreE IG: 11.2 CG: 8.6 Chronic HTN IG: 0 CG: 0 Chronic DM

Appendix E Table 1. Study Population Baseline Characteristics of Included Studies

Author, year Quality	Included populations	Excluded populations	Mean age (range)	Race/ethnicity, %	Mean BMI, kg/m2	Nulliparous %	Smoking, %	Other health behaviors and conditions, %
								IG: 0 CG: 0

Abbreviations: ABPM = Ambulatory blood pressure monitoring; AIDS = Acquired immunodeficiency syndrome; ASA = Acetylsalicylic acid; CG = Control group; DBP = Diastolic blood pressure; DM = Diabetes mellitus; Hisp = Hispanic; HTN = Hypertension; IG = Intervention group; IUGR = Intrauterine growth restriction; NR = Not reported; PreE = Preeclampsia; PI = pulsatility index; PIH = Pregnancy-induced hypertension; SGA = Small for gestational age

*Median

Appendix E Table 2. Maternal Health Outcomes, Increased Risk Population

Author, year	Outcome	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95%CI)*
CLASP, 1994[95]	Eclampsia	NR	7/4,659† (0.2)	7/4,650 (0.2)	-
Morris, 1996[107]	Eclampsia	Severe HTN developed postnatally associated with abnormal renal function and hyperuricemia, culminating in a generalized convulsion 6 days after delivery	1/52 (1.9)	0/50 (0.0)	-
Wallenburg, 1986[87]	Eclampsia	NR	0/21 (0)	1/23 (4.3)	-
Villa, 2012[104]	HELLP Syndrome	Hemolysis, elevated liver enzymes, and low platelets	0/61 (0)	1/60 (0.02)	-
Scazzacchio, 2017[106]	Incomplete HELLP syndrome‡	NR	NR	NR	-

Abbreviations: CG = Control group; CI = Confidence interval; CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; HELLP = Hemolysis, elevated liver enzymes, low platelet count; IG = Intervention group, NR = Not reported

*Dash symbol ("-") indicates insufficient data to calculate effect
† All pregnancies with data
‡ One participant in each study group developed severe preeclampsia; one with severe hypertension and the other with incomplete HELLP syndrome; authors do not specify to which study group these participants belong

Appendix E Table 3. Effect of Aspirin on Perinatal Mortality, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect
ASPRE, 2017[59]	Perinatal mortality without preeclampsia	8/798 (1.0)	14/822 (1.7)	OR*: 0.59 (99% CI: 0.19 to 1.85)
Ayala, 2012[57]	Perinatal mortality	2/176 (1.1)	5/174 (2.9)	RR†: 0.40 (95% CI: 0.08 to 2.01)
Benigni, 1989[88]	Perinatal mortality	0/17 (0.0)	1/16 (6.3)	RR†: 0.31 (95% CI: 0.01 to 7.21)
Caspi, 1994[94]	Perinatal mortality	2/48 (4.2)	2/46 (4.3)	RR†: 0.96 (95% CI: 0.14 to 6.52)
CLASP, 1994[95]	Stillbirths included all intrauterine deaths at or after 24 weeks, and neonatal deaths included all deaths after birth up to the age of 28 days.	77/4123 (1.9)	97/4134 (2.3)	RR†: 0.80 (95% CI: 0.59 to 1.07)
Davies, 1995[96]	Perinatal mortality	0/58 (0.0)	0/60 (0.0)	RR†‡: 1.03 (95% CI: 0.02 to 51.26)
Gallery, 1997[97]	Perinatal mortality	4/58 (6.9)	2/50 (4.0)	RR†: 1.72 (95% CI: 0.33 to 9.02)
Hermida, 1997[98]	Perinatal mortality	0/50 (0.0)	0/50 (0.0)	RR†‡: 1.00 (95% CI: 0.02 to 49.44)
McParland, 1990[90]	Perinatal mortality	1/48 (2.1)	3/52 (5.8)	RR†: 0.36 (95% CI: 0.04 to 3.35)
MFMU-HR, 1998[99]	Perinatal mortality	43/1254 (3.4)	56/1249 (4.5)	RR: 0.80 (95% CI: 0.50 to 1.10)
Morris, 1996[107]	Perinatal mortality	0/52 (0.0)	0/50 (0.0)	NR
Schiff, 1989[89]	Perinatal mortality	0/34 (0.0)	0/32 (0.0)	RR†‡: 0.94 (95% CI: 0.02 to 46.16)
Viinikka, 1993[93]	Perinatal mortality	2/97 (2.1)	0/100 (0.0)	RR†: 5.15 (95% CI: 0.25 to 105.98)
Wallenburg, 1986[87]	Perinatal mortality	1/21 (4.8)	1/23 (4.3)	RR†: 1.10 (95% CI: 0.07 to 16.43)
Yu, 2003[103]	Perinatal mortality	7/276 (2.5)	4/278 (1.4)	OR§: 1.89 (95% CI: 0.52 to 6.83)

Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; OR = Odds ratio; RR = Risk ratio

*Adjustment for the effect of the estimated risk for preeclampsia at screening and the participating center
†Crude calculation

Appendix E Table 3. Effect of Aspirin on Perinatal Mortality, Increased Risk Population

‡Excluded from pooled analysis.
§Adjusted for Maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch

Appendix E Table 4. Effect of Aspirin on Preterm Birth, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
ASPRE, 2017[59]	Delivery at <37 wks of gestation	53/798 (6.6)	84/822 (10.2)	RR*: 0.65 (95% CI: 0.47 to 0.90)
Ayala, 2012[57]	Delivery at <37 wks of gestation	7/176 (4.0)	20/174 (11.5)	RR*: 0.35 (95% CI: 0.15 to 0.80)
Benigni, 1989[88]	Delivery at <37 wks of gestation	2/17 (11.8)	5/16 (31.3)	RR*: 0.38 (95% CI: 0.08 to 1.67)
Caspi, 1994[94]	Delivery at <37 wks of gestation	11/24 (45.8)	14/23 (60.9)	RR*: 0.75 (95% CI: 0.44 to 1.30)
CLASP, 1994[95]	Delivery at <37 wks of gestation	686/3992 (17.2)	761/3982 (19.1)	RR*: 0.90 (95% CI: 0.82 to 0.99)
Davies, 1995[96]	Delivery at <34 wks of gestation	1/58 (1.7)	1/60 (1.7)	RR*: 1.03 (95% CI: 0.07 to 16.15)
Gallery, 1997[97]	Delivery at <37 wks of gestation	6/58 (10.3)	8/50 (16.0)	RR*: 0.65 (95% CI: 0.24 to 1.74)
Hermida,1997[98]	Delivery at <37 wks of gestation	1/50 (2.0)	5/50 (10.0)	RR*: 0.20 (95% CI: 0.02 to 1.65)
MFMU-HR, 1998[99]	Delivery at <37 wks of gestation	502/1254 (40.0)	537/1249 (43.0)	RR: 0.90 (95% CI: 0.90 to 1.00)
Morris, 1996[107]	Delivery at <37 wks of gestation	3/52 (5.8)	5/50 (10.0)	NR
Schiff, 1989[89]	Delivery at <37 wks of gestation	2/34 (5.9)	6/32 (18.8)	RR*: 0.31 (95% CI: 0.07 to 1.44)
Wallenburg, 1986[87]	Delivery at <37 wks of gestation	0/21 (0.0)	4/23 (17.4)	RR*: 0.12 (95% CI: 0.01 to 2.12)
Yu, 2003[103]	Delivery at <37 wks of gestation	67/276 (24.3)	75/278 (27.0)	OR†: 0.86 (95% CI: 0.57 to 1.29)
ASPRE, 2017[59]	Delivery at <37 wks of gestation with preeclampsia	13/798 (1.6)	35/822 (4.3)	OR‡: 0.38 (95% CI: 0.20 to 0.74)
ASPRE, 2017[59]	Delivery at <34 wks of gestation with preeclampsia	3/798 (0.4)	15/822 (1.8)	OR‡: 0.18 (99% CI: 0.03 to 1.03)

Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; OR = Odds ratio; RR = Risk ratio; wks = Weeks

*Crude calculation
†Maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch.
‡Adjustment for the effect of the estimated risk for preeclampsia at screening and the participating center

Appendix E Table 5. Effect of Aspirin on Intrauterine Growth Restriction, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
ASPRE, 2017[59]	<10th percentile	148/785 (18.9)	187/807 (23.2)	OR*: 0.77 (99% CI: 0.56 to 1.06)
Ayala, 2012[57]	Monthly echography assessments in all participants	16/176 (9.1)	32/174 (18.4)	RR†: 0.49 (95% CI: 0.28 to 0.87)
Benigni, 1989[88]	<10th percentile	2/17 (11.8)	6/16 (37.5)	RR†: 0.31 (95% CI: 0.07 to 1.33)
Caspi, 1994[94]	<10th percentile	6/48 (12.5)	11/46 (23.9)	RR†: 0.52 (95% CI: 0.21 to 1.30)
CLASP, 1994[95]	<3rd percentile	244/4123 (5.9)	272/4134 (6.6)	RR†: 0.90 (95% CI: 0.76 to 1.06)
Davies, 1995[96]	5 – 10th percentile	3/58 (5.2)	3/60 (5.0)	RR†: 1.03 (95% CI: 0.22 to 4.92)
Hermida, 1997[91]	NR	1/50 (2.0)	2/50 (4.0)	RR†: 0.50 (95% CI: 0.05 to 5.34)
McParland, 1990[90]	<5th percentile	7/48 (14.6)	7/52 (13.5)	RR†: 1.08 (95% CI: 0.41 to 2.86)
MFMU-HR, 1998[99]	<10th percentile	129/1254 (10.3)	108/1249 (8.6)	RR: 1.20 (95% CI: 0.90 to 1.50)
Morris, 1996[107]	<10th percentile	14/52 (26.9)	11/50 (22.0)	NR
Scazzocchio, 2017[106]	<10th percentile	7/80 (8.8)	13/75 (17.3)	RR†: 0.50 (95% CI: 0.21 to 1.20)
Schiff, 1989[89]	<10th percentile	2/34 (5.9)	6/31 (19.4)	RR†: 0.30 (95% CI: 0.07 to 1.40)
Viinikka, 1993[93]	Birth weight ≤2 SD	4/97 (4.1)	9/100 (9.0)	RR†: 0.46 (95% CI: 0.15 to 1.44)
Villa, 2012[104]	Birth weight <-2 SD	2/61 (3.3)	6/60 (10.0)	RR: 0.50 (95% CI: 0.10 to 1.90)
Wallenburg, 1986[87]	<10th percentile	4/21 (19.0)	6/23 (26.1)	RR†: 0.73 (95% CI: 0.24 to 2.23)
Yu, 2003[103]	<5th percentile	61/276 (22.1)	68/278 (24.5)	OR‡: 0.83 (95% CI: 0.54 to 1.28)

Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; NR = Not reported; OR = Odds ratio; RR = Risk ratio; SD = Standard deviation

Appendix E Table 5. Effect of Aspirin on Intrauterine Growth Restriction, Increased Risk Population

*Adjusted for the effect of the estimated risk for preeclampsia at screening and the participating center
†Crude calculation
‡Adjusted for maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch

Appendix E Table 6. Effect of Aspirin on Birth Weight, Increased Risk Population

Author, year	Outcome definition	IG mean (SD)	CG mean (SD)	Effect (95% CI)*
Ayala, 2012[57]	Birth weight, g	Mean: 3286 (519)	Mean: 3162 (580)	Calc MeanDiff: 124.00 (95% CI: 8.72 to 239.28)
Benigni, 1989[88]	Birth weight, g	Mean: 2922 (599)	Mean: 2264 (1072)	Calc MeanDiff: 658.00 (95% CI: 70.24 to 1245.76)
Caspi, 1994[94]	Birth weight, g	Mean: 2502 (561)	Mean: 2108 (542)	Calc MeanDiff: 394.00 (95% CI: 170.86 to 617.14)
CLASP, 1994[95]	Birth weight, g	Mean: 3024 (788)	Mean: 2991 (810)	MeanDiff: 32.00 (95% CI: 0.00 to 64.00)
Gallery, 1997[97]	Birth weight, g+	Mean: 3291 (514.3928)	Mean: 3029 (714.1779)	Calc MeanDiff: 262.00 (95% CI: 24.09 to 499.91)
Grab, 2000[101]	Birth weight, g	Median: 3150 (Range: 560 to 3770)	Median: 2900 (Range: 800 to 4070)	-
Hermida, 1997[98]	Birth weight, g	Mean: 3265 (452.5483)	Mean: 3155 (678.8225)	Calc MeanDiff: 110.00 (95% CI: -116.14 to 336.14)
McParland, 1990[90]	Birth weight, g	Mean: 3068 (555)	Mean: 2954 (852)	Calc MeanDiff: 114.00 (95% CI: -170.39 to 398.39)
Morris, 1996[107]	Birth weight, g	Mean: 3145 (633)	Mean: 3049 (576)	NR
Scazzocchio, 2017[106]	Birth weight, g	Mean: 3112 (526)	Mean: 3117 (529)	Calc MeanDiff: -5.00 (95% CI: -171.16 to 161.16)
Schiff, 1989[89]	Adjusted birth weight percentile†	Mean: 43.9 (13.7)	Mean: 38.6 (12.2)	Calc MeanDiff: 5.30 (95% CI: -1.03 to 11.63)
Schiff, 1989[89]	Birth weight, g	Mean: 3037 (NR)	Mean: 2706 (NR)	-
Viinikka, 1993[93]	Birth weight, g	Mean: 3348 (707)	Mean: 3170 (665)	Calc MeanDiff: 178.00 (95% CI: -13.61 to 369.61)
Villa, 2012[104]	Birth weight, g	Mean: 3413 (630)	Mean: 3321 (871)	Calc MeanDiff: 92.00 (95% CI: -178.52 to 362.52)
Wallenburg, 1986[87]	Birth weight, g	Median: 3190 (Range: 2380 to 4320)	Median: 3040 (Range: 530 to 4035)	-

Abbreviations: Calc MeanDiff = Calculated Mean Difference; CG = Control group; CI = Confidence interval; IG = Intervention group; SD = Standard deviation

*Dash symbol ("-") indicates insufficient data to calculate effect
†Adjusted for gestational age at delivery

Appendix E Table 7. Effect of Aspirin on Gestational Age, Increased Risk Population

Author, year	Outcome description	IG mean (SD)	CG mean (SD)	Effect (95% CI)*
Ayala, 2012[57]	Monthly echography assessments in all participants	Mean: 39.5 (1.6)	Mean: 39.2 (1.9)	Calc MeanDiff: 0.30 (95% CI: -0.07 to 0.67)
Benigni, 1989[88]	Duration of pregnancy (weeks)	Mean: 39 (2)	Mean: 35 (4)	Calc MeanDiff: 4.00 (95% CI: 1.86 to 6.14)
Caspi, 1994[94]	Gestational age at birth (wk), mean; gestational age was determined by last menstrual period, ovulation or ovum pickup in in vitro fertilization (NF) cases, and confirmed by first or early second trimester ultrasound scan	Mean: 36 (31)	Mean: 35 (2.3)	Calc MeanDiff: 1.00 (95% CI: -11.71 to 13.71)
CLASP, 1994[95]	Average duration of pregnancy (weeks)	Mean: 38.15 (3.82)	Mean: 37.99 (3.93)	Calc MeanDiff: 0.16 (95% CI: 0.00 to 0.32)
Davies, 1995[96]	Mean age of birth (weeks)	Mean: 39.9 (NR)	Mean: 39.6 (NR)	-
Gallery, 1997[97]	Mean gestational age at delivery (calculated without 4 intrauterine deaths, as the extent of postmortem weight alteration could not be assessed)	Mean: 38.6 (1.469694)	Mean: 37.5 (2.828427)	Calc MeanDiff: 1.10 (95% CI: 0.24 to 1.96)
Grab, 2000[101]	Gestational age at delivery (wks)	Median: 39.7 (Range: 26.6 to 42.1)	Median: 38.6 (Range: 28.3 to 41.4)	-
Hermida, 1997[98]	Gestational age at delivery (wks)	Mean: 39.6 (1.414214)	Mean: 39.4 (2.12132)	Calc MeanDiff: 0.20 (95% CI: -0.51 to 0.91)
McParland, 1990[90]	Gestation at delivery (wks)	Mean: 39.5 (2.1)	Mean: 38.7 (3.9)	Calc MeanDiff: 0.80 (95% CI: -0.44 to 2.04)
Schiff, 1989[89]	Gestational age at birth (wks)	Mean: 38.9 (1.14)	Mean: 37.3 (.86)	Calc MeanDiff: 1.60 (95% CI: 1.11 to 2.09)

Appendix E Table 7. Effect of Aspirin on Gestational Age, Increased Risk Population

Author, year	Outcome description	IG mean (SD)	CG mean (SD)	Effect (95% CI)*
Viinikka, 1993[93]	Age of gestation at delivery (weeks)	Mean: 38.6 (2.1)	Mean: 38.2 (2)	Calc MeanDiff: 0.40 (95% CI: -0.17 to 0.97)
Wallenburg, 1986[87]	Week of delivery	Median: 40 (Range: 37 to 42)	Median: 39 (Range: 30 to 43)	-

Abbreviations: Calc MeanDiff = Calculated Mean Difference; CG = Control group; CI = Confidence interval; IG = Intervention group; SD = Standard deviation

*Dash symbol ("-") indicates insufficient data to calculate effect

Appendix E Table 8. Effect of Aspirin on Preeclampsia, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
ASPRE, 2017[59]	SBP ≥140 mmHg and/or DBP ≥90 mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. HTN should be accompanied by proteinuria ≥300 mg in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In preeclampsia superimposed on chronic HTN significant proteinuria (as defined above) should develop after 20 weeks' gestation in women with known chronic HTN (history of HTN before conception or the presence of HTN at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease)	66/798 (8.3)	94/822 (11.4)	RR*: 0.72 (95% CI: 0.54 to 0.98)
Ayala, 2012[57] (657)	Hyperbaric index consistently above the threshold for diagnosis of HTN in pregnancy after the 20th wk of gestation and proteinuria, ≥300 mg/24-h urine, diagnosed after the 20th wk of gestation in a previously normotensive woman	11/176 (6.3)	22/174 (12.6)	RR*: 0.49 (95% CI: 0.25 to 0.99)
Caspi, 1994[94] (114)	Sustained elevation of more than 15 mmHg of DBP or 30 mmHg of SBP (on at least two occasions six or more hours apart) compared to levels in the second trimester before treatment, presence of proteinuria of more than 300 mg per day (in the absence of urinary tract infection associated with HTN)	0/24 (0.0)	2/23 (8.7)	RR*: 0.19 (95% CI: 0.01 to 3.80)
CLASP, 1994 [95]	Development of HTN and proteinuria after randomization. For those with baseline DBP below 90 mmHg, HTN defined as a rise of at least 25 mmHg, to 90 mmHg or higher. For those with an initial DBP of 90 mmHg or above, an increment of at least 15 mmHg was required. Proteinuria defined as the appearance after randomization of at least 1+ on protein stick-testing during pregnancy, without evidence of urinary tract infection.	267/3992 (6.7)	302/3982 (7.6)	RR*: 0.88 (95% CI: 0.75 to 1.03)
Davies, 1995[96]	Two DBP readings of >90 mmHg at least 6 hours apart or a single reading of >110 mmHg, proteinuria defined as + + on reagent strip testing or greater than 300 mg/L in a 24-h urine collection.	5/58 (8.6)	7/60 (11.7)	OR: 0.70 (95% CI: 0.20 to 2.40)
Grab, 2000[101]	Proteinuric HTN	3/22 (13.6)	2/21 (9.5)	RR*: 1.43 (95% CI: 0.27 to 7.73)

Appendix E Table 8. Effect of Aspirin on Preeclampsia, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
Hermida, 1997[98]	Gestational HTN and proteinuria, above 300 mg/24 h, with or without edema	3/50 (6.0)	7/50 (14.0)	RR*: 0.43 (95% CI: 0.12 to 1.56)
McParland, 1990[90]	Proteinuric HTN, specific SBP/DBP, proteinuria not defined	1/48 (2.1)	10/52 (19.2)	RR*: 0.11 (95% CI: 0.01 to 0.81)
MFMU-HR, 1998[99]	Women who did not have HTN or proteinuria at BL who developed HTN plus one of the following: proteinuria, thrombocytopenia, or pulmonary edema. HTN defined as either SBP ≥ 140 mmHg or DBP ≥ 90 mmHg on two occasions at least 4 hours apart. Proteinuria defined as excretion of 300 mg of protein in a 24-hour urine collection, or two dipstick-test results of ≥2 + (≥100 mg per deciliter), the values recorded at least four hours apart, with no evidence of urinary tract infection. Thrombocytopenia defined as a platelet count of less than 100,000 per cubic millimeter.	226/1254 (18.0)	250/1249 (20.0)	RR: 0.90 (95% CI: 0.80 to 1.10)
Morris, 1996[107]	PIH plus proteinuria (1+ or more on dipstick testing on at least two occasions 6 hours apart) or hyperuricemia	4/52 (7.7)	7/50 (14.0)	NR
Scazzocchio, 2017[106]	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg on two readings at least four hours apart in previously normotensive women after 20 weeks gestation, and proteinuria >300 mg/24 hr	4/80 (5.0)	3/75 (4.0)	RR*: 1.25 (95% CI: 0.29 to 5.40)
Scazzocchio, 2017[106]	Severe preeclampsia, defined as: BP ≥ 160/110 mmHg on two or more occasions, proteinuria ≥ 5g/24 hr, or the presence of maternal complications including: eclampsia, HELLP syndrome (lactate dehydrogenase > 600 IU/L, aspartate transaminase > 62 IU/L, platelet count <100 x 10^9/L), acute renal failure (creatinine > 1.2 mg/dL), subcapsular hepatic hematoma, pulmonary edema, placental abruption, or the presence of disseminated intravascular disease	1/80 (1.3)	1/75 (1.3)	RR*: 0.94 (95% CI: 0.06 to 14.72)

Appendix E Table 8. Effect of Aspirin on Preeclampsia, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
Schiff, 1989[89]	SBP > 140 mmHg, DBP > 90 mmHg, or both when measured on at least two occasions within 24 hours of each other; accompanied by proteinuria (>1 g in 24 hours)	1/34 (2.9)	7/31 (22.6)	RR*: 0.13 (95% CI: 0.02 to 1.00)
Viinikka, 1993[93]	Exacerbation of preexisting HTN (>160/120 mmHg) or the emergence of HTN (>160/110 mmHg) in women normotensive before pregnancy, and proteinuria > 300 mg/24 hours.	9/97 (9.3)	11/100 (11.0)	RR*: 0.84 (95% CI: 0.37 to 1.95)
Villa, 2012[104]	Blood pressure > or equal to 140 and/or 90 mmHg in two consecutive measurements and proteinuria > or equal to 0.3 g/24 hours	8/61 (13.1)	11/60 (18.3)	RR: 0.80 (95% CI: 0.40 to 1.80)
Villa, 2012[104]	Early preeclampsia; preeclampsia diagnosed before 34 + 0 weeks of gestation	1/61 (1.6)	4/60 (6.7)	RR: 0.50 (95% CI: 0.10 to 2.60)
Villa, 2012[104]	Preterm preeclampsia; preeclampsia diagnosed before 37 + 0 weeks of gestation	3/61 (4.9)	5/60 (8.3)	RR: 0.80 (95% CI: 0.20 to 2.80)
Villa, 2012[104]	SBP ≥160 and/or DBP ≥110 and/or proteinuria ≥5 g/24 hours)	3/61 (4.9)	8/60 (13.3)	RR: 0.50 (95% CI: 0.20 to 1.60)
Wallenburg, 1986[87]	DBP >95 mmHg on at least two occasions six or more hours apart and concomitant proteinuria (0.5 g/L) in the absence of a urinary tract infection	0/21 (0.0)	7/23 (30.4)	RR*: 0.07 (95% CI: 0.00 to 1.20)
Yu, 2003[103]	Two recordings of DBP of 90 mmHg or higher at least four hours apart or one recording of DBP of at least 120 mmHg, in a previously normotensive woman, and a urine protein excretion of at least 300 mg in 24h or two readings of 2+ or higher on dipstick analysis of midstream or catheter urine specimens if no 24h collection is available.	49/276 (17.8)	52/278 (18.7)	OR†: 0.88 (95% CI: 0.56 to 1.40)

Abbreviations: BL = Baseline; CG = Control group; CI = Confidence interval; DBP = Diastolic blood pressure; HELLP = Hemolysis, Elevated Liver enzyme levels, and Low Platelet levels; hr = Hour; IG = Intervention group; SBP = Systolic blood pressure; OR = Odds ratio; RR = Risk ratio

*Crude calculation

†Adjusted for maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch.

Appendix E Table 9. Effect of Aspirin on Gestational Hypertension, Increased Risk Population

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
ASPRE, 2017[59]	SBP should be 140 mmHg or more and/or the DBP should be 90 mmHg or more on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women.	80/798 (10.0)	69/822 (8.4)	RR*: 1.19 (95% CI: 0.88 to 1.62)
Ayala, 2012[57]	Hyperbaric index (HBI): total area of BP excess summed over the 24-h period above the upper limit of the time-varying tolerance interval calculated as a function of gestational age; consistently above the threshold for diagnosis of HTN in pregnancy after the 20th wk of gestation	26/176 (14.8)	49/174 (28.2)	RR*: 0.52 (95% CI: 0.34 to 0.80)
Benigni, 1989[88]	Pregnancy-induced HTN, blood pressure levels higher than 140/90 mmHg in women whose blood pressure had previously been normal.	0/17 (0.0)	3/16 (18.8)	RR*: 0.13 (95% CI: 0.01 to 2.42)
Caspi, 1994[94]	Sustained elevation of more than 15 mmHg of DBP or 30 mmHg of SBP (on at least two occasions 6 or more hours apart) compared to levels in the second trimester before treatment.	1/24 (4.2)	6/23 (26.1)	RR*: 0.16 (95% CI: 0.02 to 1.23)
Davies, 1995[96]	Two DBP readings of > 90 mmHg at least 6 hours apart or a single reading of > 110 mmHg	2/58 (3.4)	4/60 (6.7)	RR*: 0.52 (95% CI: 0.10 to 2.72)
Hermida, 1997[98]	Conventional BP values above 140/90 mmHg for systolic/diastolic BP without clinical record of HTN previous to pregnancy	5/50 (10.0)	9/50 (18.0)	RR*: 0.56 (95% CI: 0.20 to 1.54)
McParland, 1990[90]	Pregnancy-induced HTN; specific SBP/DPB not defined	6/48 (12.5)	13/52 (25.0)	RR*: 0.50 (95% CI: 0.21 to 1.21)
Morris, 1996[107]	Antenatal blood pressure > 140/90, with a rise in DBP of at least 15 mmHg on at least two occasions 6 hours apart	8/52 (15.4)	7/50 (14.0)	NR
Villa, 2012[104]	New onset HTN after 20 weeks gestation	10/61 (16.4)	6/60 (10.0)	RR: 1.40 (95% CI: 0.60 to 3.50)

Abbreviations: CI = Confidence interval; CG = Control group; DBP = Diastolic blood pressure; HBI = Hyperbaric index; HTN = Hypertension; IG = Intervention group; RR = Risk ratio; SBP = Systolic blood pressure; wk = Week

*Crude calculation

Appendix E Table 10. Harms of Maternal Bleeding, Average and Increased Risk Populations

Author, year	Outcome	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
Ayala, 2012[57]	Antepartum hemorrhage	NR	6/176 (3.4)	9/174 (5.2)	RR*: 0.66 (95% CI: 0.24 to 1.81)
MFMU-LR, 1993[92]	Bleeding During Delivery	Excessive blood loss (>500 mL for vaginal delivery and >1000 mL for a cesarean delivery)	102/1485 (6.9)	109/1500 (7.3)	RR*: 0.95 (95% CI: 0.73 to 1.23)
CLASP, 1994[95]	Blood Transfusion Required	NR	188/4659 (4.0)	147/4650 (3.2)	
Mone, 2018[105]	Blood Transfusion Required	NR	3/192 (1.6)	4/354 (1.1)	OR: 0.50 (95% CI: 0.10 to 2.70)
Morris, 1996[107]	Antepartum hemorrhage	NR	2/52 (3.8)	1/50 (2.0)	NR
Rotchell, 1998[100]	Blood Transfusion Required	NR	19/1819 (1.0)	18/1822 (1.0)	
MFMU-LR, 1993[92]	Blood Transfusion Required	NR	7/1485 (0.5)	10/1500 (0.7)	RR*: 0.71 (95% CI: 0.27 to 1.85)
Subtil, 2003[102]	Blood Transfusion Required	NR	3/1634 (0.2)	9/1640 (0.5)	
Yu, 2003[103]	Blood Transfusion Required	NR	6/276 (2.2)	7/278 (2.5)	
Ayala, 2012[57]	Postpartum hemorrhage	NR	3/176 (1.7)	6/174 (3.4)	RR*: 0.49 (95% CI: 0.13 to 1.95)
CLASP, 1994[95]	Postpartum hemorrhage	Placental bleed ≥500 mL	1200/4659 (25.8)	1182/4650 (25.4)	RR*: 1.01 (95% CI: 0.95 to 1.09)
Hermida, 1997[98]	Postpartum hemorrhage	Antepartum hemorrhage, no complication with maternal bleeding	0/50 (0.0)	0/50 (0.0)	RR*†: 1.00 (95% CI: 0.02 to 49.44)
MFMU-HR, 1998[99]	Postpartum hemorrhage	NR	73/1254 (5.8)	77/1249 (6.2)	RR: 0.90 (95% CI: 0.70 to 1.30)
Mone, 2018[105]	Postpartum hemorrhage	>500 mL blood loss	25/179 (14.0)	9/183 (4.9)	RR*: 2.84 (95% CI: 1.36 to 5.91)
Mone, 2018[105]	Postpartum hemorrhage	>1000 mL blood loss	7/179 (3.9)	5/183 (2.7)	RR*: 1.43 (95% CI: 0.46 to 4.43)
Rotchell, 1998[100]	Postpartum hemorrhage	≥500 mL blood loss	178/1819 (9.8)	175/1822 (9.6)	RR*: 1.02 (95% CI: 0.84 to 1.24)
Scazzocchio, 2017[106]	Postpartum hemorrhage	NR	2/80 (2.5)	5/75 (6.7)	RR*: 0.38 (95% CI: 0.08 to 1.87)

Appendix E Table 10. Harms of Maternal Bleeding, Average and Increased Risk Populations

Author, year	Outcome	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
MFMU-LR, 1993[92]	Postpartum hemorrhage	NR	45/1485 (3.0)	37/1500 (2.5)	RR*: 1.23 (95% CI: 0.80 to 1.89)
Subtil, 2003[102]	Postpartum hemorrhage	≥500 mL blood loss	63/1634 (3.9)	49/1640 (3.0)	RR*: 1.29 (95% CI: 0.89 to 1.86)
Wallenburg, 1986[87]	Postpartum hemorrhage	Postpartum hemorrhage	0/21 (0.0)	0/23 (0.0)	RR*†: 1.09 (95% CI: 0.02 to 52.67)
Yu, 2003[103]	Postpartum hemorrhage	>500 mL blood loss	73/276 (26.4)	71/278 (25.5)	OR‡: 1.09 (95% CI: 0.73 to 1.62)

Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; NR = Not reported; OR = Odds ratio; RR = Risk ratio

*Crude calculation
†Excluded in the pooled metanalysis.
‡Adjusted for maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch.

Appendix E Table 11. Harms of Placental Abruption, Average and Increased Risk Populations

Author, year	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
ASPRE, 2017[59]	Placental abruption without preeclampsia	4/798 (0.5)	6/822 (0.7)	RR*: 0.69 (95% CI: 0.19 to 2.42)
Caspi, 1994[94]	Placental abruption	0/24 (0.0)	0/23 (0.0)	RR*†: 0.96 (95% CI: 0.02 to 46.47)
CLASP, 1994[95]	Placental abruption	86/4659 (1.8)	71/4650 (1.5)	RR*: 1.21 (95% CI: 0.89 to 1.65)
Davies, 1995[96]	Placental abruption	2/58 (3.4)	1/60 (1.7)	OR: 1.24 (95% CI: 0.20 to 23.90)
Hauth, 1993[91]	Placental abruption	1/302 (0.3)	0/302 (0.0)	RR*: 3.00 (95% CI: 0.12 to 73.35)
Hermida, 1997[98]	Placental abruption	0/50 (0.0)	0/50 (0.0)	RR*†: 1.00 (95% CI: 0.02 to 49.44)
MFMU-HR, 1998[99]	Diagnosed according to clinical criteria: vaginal bleeding, uterine tenderness, as well as examination of the placenta.	17/1254 (1.4)	25/1249 (2.0)	RR: 0.70 (95% CI: 0.40 to 1.30)
Mone, 2018[105]	Placental abruption	1/179 (0.6)	0/183 (0.0)	RR*: 3.07 (95% CI: 0.13 to 74.78)
Rotchell, 1998[100]	Placental abruption	9/1819 (0.5)	14/1822 (0.8)	RR*: 0.64 (95% CI: 0.28 to 1.48)
MFMU-LR, 1993[92]	Diagnosed according to clinical findings (vaginal bleeding, uterine tenderness) or placental examination	11/1485 (0.7)	2/1500 (0.1)	RR: 5.56 (95% CI: 1.24 to 25.06)
Subtil, 2003[102]	Placental abruption either clinical or detected in a pathology examination of the placenta	13/1634 (0.8)	9/1640 (0.5)	RR: 1.45 (95% CI: 0.62 to 3.38)
Viinikka, 1993[93]	Placental abruption	0/97 (0.0)	0/100 (0.0)	RR*†: 1.03 (95% CI: 0.02 to 51.43)
Yu, 2003[103]	Placental abruption	10/276 (3.6)	5/278 (1.8)	OR‡: 2.54 (95% CI: 0.78 to 8.21)

Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; OR = Odds ratio; RR = Risk ratio

*Crude calculation
†Exclude in the pooled metanalysis.
‡Adjusted for maternal age, parity, ethnicity, education, smoking status, partner, previous pre-eclampsia, family history of pre-eclampsia, body mass index, blood pressure at randomization, mean pulsatility index, and the presence of unilateral or bilateral notch.

Appendix E Table 12. Perinatal Harms, Average and Increased Risk Populations

Author, year	Outcome	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
MFMU-LR, 1993[92]	Any bleeding disorder	Any bleeding disorder (infant)	104/1480 (7.0)	98/1505 (6.5)	RR*: 1.08 (95% CI: 0.83 to 1.41)
Schiff, 1989[89]	Cephalohematoma	Cephalohematoma	0/34 (0.0)	1/32 (3.1)	RR*: 0.31 (95% CI: 0.01 to 7.45)
MFMU-LR , 1993[92]	Cephalohematoma	Cephalohematoma	68/1480 (4.6)	55/1505 (3.7)	RR*: 1.26 (95% CI: 0.89 to 1.78)
ASPRE, 2017[59]	Congenital malformations	Fetal structural defects	8/798 (1.0)	16/822 (1.9)	RR*: 0.52 (95%CI -0.34 to 1.36)
Gallery, 1997[97]	Congenital malformations	Congenital malformations	2/54 (3.7)	4/50 (8.0)	RR*: 0.46 (95% CI: 0.09 to 2.42)
Mone, 2018[105]	Congenital malformations	Total congenital anomaly (includes cardiac, GI, neurological, renal)	3/179 (1.7)	4/183 (2.2)	RR*: 0.77 (95% CI: 0.17 to 3.38)
Viinikka, 1993[93]	Congenital malformations	Fetal anencephaly	1/97 (1.0)	0/100 (0.0)	RR*: 3.09 (95% CI: 0.13 to 74.98)
ASPRE, 2017[59]	Fetal intracranial bleeding	Intraventricular hemorrhage of grade ≥II	2/798 (0.3)	1/822 (0.1)	OR†: 2.23 (99% CI: 0.09 to 52.70)
Benigni, 1989[88]	Fetal intracranial bleeding	Intracranial hemorrhage	0/17 (0.0)	0/16 (0.0)	RR*: 0.94 (95% CI: 0.02 to 44.98)
MFMU-HR, 1998[99]	Fetal intracranial bleeding	Defined according to ultrasound criteria	21/1254 (1.7)	14/1249 (1.1)	RR: 1.50 (95% CI: 0.80 to 2.80)
MFMU-LR , 1993[92]	Fetal intracranial bleeding	Cerebral hemorrhage	10/1480 (0.7)	11/1505 (0.7)	RR*: 0.92 (95% CI: 0.39 to 2.17)
CLASP, 1994[95]	Fetal intracranial bleeding	Intraventricular hemorrhage	33/4810 (0.7)	45/4821 (0.9)	RR*: 0.74 (95% CI: 0.47 to 1.15)
Rotchell, 1998[100]	Fetal intracranial bleeding	Intraventricular hemorrhage	0/1834 (0.0)	1/1841 (0.1)	RR*: 0.33 (95% CI: 0.01 to 8.21)
Schiff, 1989[89]	Fetal intracranial bleeding	Intraventricular hemorrhage	0/34 (0.0)	0/32 (0.0)	RR*: 0.94 (95% CI: 0.02 to 46.16)
Subtil, 2003[102]	Fetal intracranial bleeding	Intraventricular hemorrhage grade II, III, or IV	1/1645 (0.1)	6/1660 (0.4)	RR*: 0.17 (95% CI: 0.02 to 1.40)
ASPRE, 2017[59]	Respiratory distress syndrome	Respiratory distress syndrome treated with surfactant and ventilation	11/798 (1.4)	22/822 (2.7)	OR†: 0.53 (99% CI: 0.20 to 1.40)

Appendix E Table 12. Perinatal Harms, Average and Increased Risk Populations

Author, year	Outcome	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
Gallery, 1997[97]	Severe hyaline membrane disease	Neonatal death caused by severe hyaline membrane disease	0/58 (0.0)	1/50 (2.0)	RR*: 0.29 (95% CI: 0.01 to 6.92)
Gallery, 1997[97]	Staphylococcus epidermis septicemia	One neonatal death from Staphylococcus epidermis septicemia	0/58 (0.0)	1/50 (2.0)	RR*: 0.29 (95% CI: 0.01 to 6.92)

Abbreviations: CG = Control group; CI = Confidence interval; GI = Gastrointestinal; IG = Intervention group; OR = Odds ratio; RR = Risk ratio

*Crude calculation
†Adjustment for the effect of the estimated risk for preeclampsia at screening and the participating center
Abbreviations: CG = Control group; IG = Intervention group

Appendix E Table 13. Longer Term Followup Outcomes Among Infants Born to CLASP Trial Participants

Study, Year Quality	Treatment group	N Analyzed	Child outcomes, n (%)
CLASP, 1994[95] Good 18-month followup	IG	2,146	*Gross motor failure:* 9 (0.4) *Fine motor failure:* 28 (1.3) *Height <3rd percentile:* 236 (11.0) *Weight <3rd percentile:* 112 (5.2)
	CG	2,219	*Gross motor failure:* 10 (0.5) *Fine motor failure:* 39 (1.8) *Height <3rd percentile:* 248 (11.2) *Weight <3rd percentile:* 129 (5.8)

Appendix E Table 14. Other Maternal Outcomes, Average and Increased Risk Populations

Author, year	Outcome	Outcome definition	IG n/N (%)	CG n/N (%)	Effect (95% CI)
Mone, 2018[105]	Any Adverse Event	NR	123/192 (64.1)	143/354 (40.4)	OR: 2.60 (95% CI: 1.80 to 3.80)
Mone, 2018[105]	Serious Adverse Event	NR	32/179 (17.9)	28/183 (15.3)	RR*: 1.17 (95% CI: 0.74 to 1.86)
Morris, 1996[107]	Any Adverse Event	NR	29/52 (55.7)	28/50 (56.0)	NR
ASPRE, 2017[59]	Maternal death	Maternal death due to pulmonary embolism	0/798 (0.0)	1/822 (0.1)	RR*: 0.34 (95% CI: 0.01 to 8.42)
Hauth, 1993[91]	Preterm Rupture of Membranes	Preterm premature rupture of membranes	9/302 (3.0)	8/302 (2.6)	RR*: 1.13 (95% CI: 0.44 to 2.88)
MFMU-LR , 1993[92]	Preterm Rupture of Membranes	Premature rupture of membranes with preterm delivery	49/1485 (3.3)	54/1500 (3.6)	RR*: 0.92 (95% CI: 0.63 to 1.34)

Abbreviations: CG = Control group; CI = Confidence interval; IG = Intervention group; NR = Not reported; OR = Odds ratio; RR = Risk ratio

*Crude calculation

Appendix F Table 1. Within Trial Subgroup Differences in Aspirin Effectiveness Based on Reported Tests for Interaction

Study	Outcome	Subgroup Comparison	N	IG n/N (%)	CG n/N (%)	RR or OR (95%CI)	P value for interaction test*
CLASP, 1994[95]	Preeclampsia	Aspirin ≤20 weeks' gestation	5482	176/2733 (6.4)	222/2749 (8.1)	0.79 (0.66, 0.96)	NS (0.06)†
		Aspirin >20 week's gestation	2492	91/1259 (7.2)	80/1233 (6.5)	1.11 (0.83, 1.45)	
		Nulliparous	1837	57/922 (6.2)	62/975 (6.8)	0.91 (0.64, 1.29)	NS
		Multiparous	6137	210/3070 (6.8)	240/3067 (7.8)	0.87 (0.73, 1.04)	
	Preterm birth (<37 weeks gestation)	Aspirin ≤20 weeks' gestation	5482	477/2733 (17.5)	497/2749 (18.1)	0.97 (0.86, 1.08)	NS (0.03)†
		Aspirin >20 week's gestation	2492	209/1259 (16.6)	264/1233 (21.4)	0.78 (0.66, 0.91)	
		Nulliparous	1837	144/922 (15.6)	184/915 (20.1)	0.77 (0.64, 0.95)	NS
		Multiparous	6137	542/3070 (17.7)	577/3067 (18.8)	0.94 (0.84, 1.04)	
	Perinatal mortality	Entered study ≤20 weeks' gestation	5635	55/2802 (2.0)	62/2833 (2.2)	0.89 (0.63, 1.28)	NS
		Entered study >20 week's gestation	2622	22/1321 (1.7)	35/1301 (2.7)	0.62 (0.37, 1.05)	
		Nulliparous	1961	11/981 (1.1)	22/980 (2.2)	0.50 (0.24, 1.02)	NS
		Multiparous	6296	66/3142 (2.1)	75/3154 (2.4)	0.88 (0.64, 1.23)	
	IUGR	Aspirin ≤20 weeks' gestation	5635	151/2802 (5.4)	185/2833 (6.5)	0.82 (0.67, 1.02)	NS
		Aspirin >20 week's gestation	2622	93/1321 (7.0)	87/1301 (6.7)	1.05 (0.79, 1.40)	
		Nulliparous	1961	53/981 (5.4)	63/980 (6.4)	0.84 (0.59, 1.20)	NS
		Multiparous	6296	191/3142 (6.1)	209/3154 (6.6)	0.92 (0.76, 1.11)	
MFMU-HR, 1998[99‡]	Preeclampsia§	Pregestational diabetes risk group	462	(18)	(22)	0.9 (0.6.1.2)	NS‖
		Hypertension risk group	763	(26)	(25)	1.1 (0.8, 1.4)	
		Multifetal gestation risk group	678	(12)	(16)	0.7 (0.5, 1.1)	
		Previous preeclampsia risk group	600	(17)	(19)	0.9 (0.6, 1.2)	
		Race White	814	(18)	(22)	0.8 (0.6, 1.1)	NS‖
		Race nonWhite	1689	(18)	(20)	0.9 (0.8, 1.2)	
		Nulliparous	668	(25)	(27)	0.9 (0.7, 1.2)	NS‖
		Multiparous	1835	(16)	(18)	0.9 (0.7, 1.1)	
		Systolic BP <120 mmHg at entry¶	1151	(11)	(14)	0.8 (0.6, 1.1)	NS‖

Appendix F Table 1. Within Trial Subgroup Differences in Aspirin Effectiveness Based on Reported Tests for Interaction

Study	Outcome	Subgroup Comparison	N	IG n/N (%)	CG n/N (%)	RR or OR (95%CI)	P value for interaction test*
		Systolic BP 120–134 mmHg at entry‖	435	(22)	(26)	0.8 (0.6, 1.2)	
		Aspirin <16 weeks' gestation	461	49/225 (21.8)	55/236 (23.3)	0.93 (0.67, 1.31)	0.87
		Aspirin ≥16 weeks' gestation	2042	182/1029 (17.7)	199/1013 (19.6)	0.90 (0.75, 1.08)	
		BMI <30	1512	131/756 (17.3)	144/756 (19.1)	0.91 (0.7, 1.13)	0.85
		BMI ≥30	967	97/487 (19.9)	108/480 (22.5)	0.89 (0.7, 1.13)	
		Nonsmokers	2079	203/1041 (19.5)	218/1038 (21.0)	0.93 (0.78, 1.10)	0.58
		Smokers	421	29/214 (13.6)	35/207 (16.9)	0.80 (0.51, 1.26)	
	Preterm birth (<37 weeks gestation)	Nonsmokers	2079	465/1038 (44.8)	512/1041 (49.2)	0.91 (0.84, 0.99)	0.01
		Smokers	421	100/214 (46.5)	113/207 (54.5)	1.17 (0.99, 1.39)	
	SGA	Nonsmokers	2079	74/1038 (7.1)	74/1041 (7.1)	1.0 (0.7, 1.4)	0.36
		Smokers	421	175/1252 (14.0)	132/1248 (10.6)	1.3 (0.8, 2.2)	
ASPRE, 2017[59#]	Preterm birth with preeclampsia	Maternal age <30 years	649	7/321 (2.2)	14/331 (4.2)	0.51 (0.20, 1.32)	0.41
		Maternal age≥30 years	971	6/477 (1.3)	21/491 (4.3)	0.29 (0.11, 0.75)	
		BMI <25 kg/m^2	649	5/311 (1.0)	14/338 (4.1)	0.34 (0.12, 0.99)	0.60
		BMI ≥25 kg/m^2	971	8/487 (1.6)	21/484 (4.3)	0.41 (0.18, 0.96)	
		Racial origin Afro Caribbean	409	5/208 (2.4)	11/201 (5.5)	0.45 (0.15, 1.39)	0.91
		Racial origin Caucasian	1087	7/528 (1.3)	22/559 (3.9)	0.34 (0.14, 0.82)	
		Racial origin Other	124	1/62 (0.18)	2/62 (3.2)	0.41 (0.04, 4.85)	
		Method conception natural	1526	12/747 (1.6)	32/779 (4.1)	0.40 (0.20, 0.79)	0.13
		Method conception assisted	94	1/51 (2.0)	3/43 (7.0)	0.19 (0.02, 2.05)	
		Nonsmokers	1504	12/741 (1.6)	32/763 (4.2)	0.39 (0.20, 0.78)	0.79
		Smokers	116	1/57 (1.8)	3/59 (5.1)	0.28 (0.03, 3.04)	
		Family history preeclampsia	166	2/76 (2.6)	5/90 (5.6)	0.37 (0.18, 2.75)	0.77
		No family history of preeclampsia	1454	11/722 (1.5)	30/732 (4.1)	0.49 (0.09, 2.73)	
		Nulliparous	1090	7/547 (1.3)	24/543 (4.4)	0.27 (0.11, 0.64)	0.39

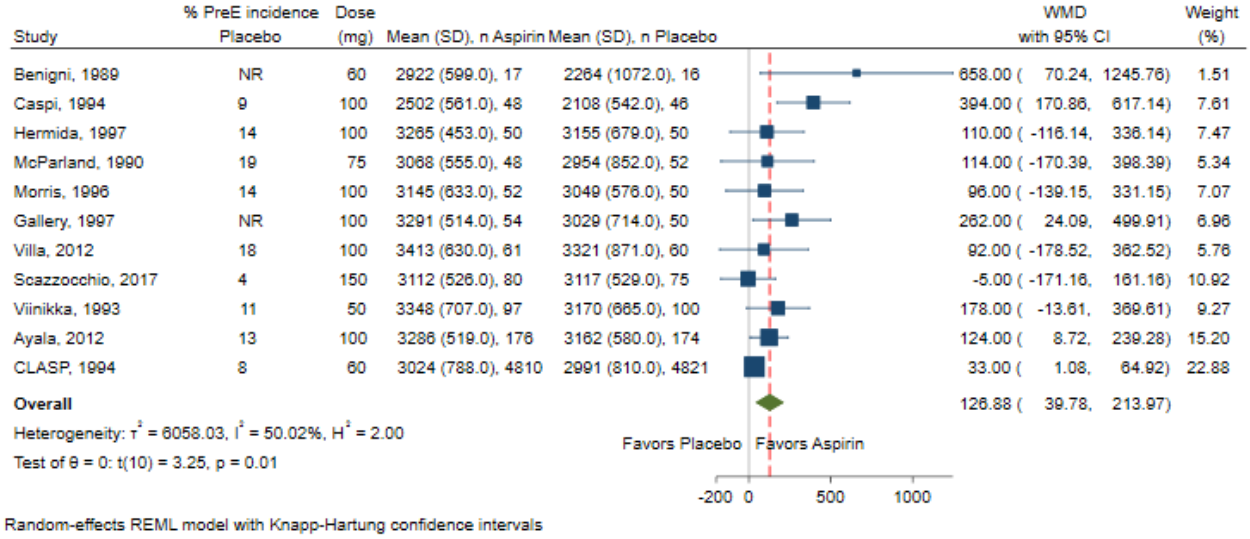
Appendix F Table 1. Within Trial Subgroup Differences in Aspirin Effectiveness Based on Reported Tests for Interaction

Study	Outcome	Subgroup Comparison	N	IG n/N (%)	CG n/N (%)	RR or OR (95%CI)	P value for interaction test*
		Multiparous without preeclampsia	359	4/164 (2.4)	7/195 (3.6)	0.79 (0.22, 2.90)	
		Multiparous with preeclampsia	171	2/87 (2.3)	4/84 (4.8)	0.50 (0.08, 2.93)	
		History of chronic hypertension	110	5/49 (10.2)	5/61 (8.2)	1.30 (0.33, 5.12)	NS (0.06)[#]
		No history of chronic hypertension	1510	8/749 (1.1)	30/761 (3.9)	0.27 (0.12, 0.60)	

Abbreviations: BMI = Body mass index; CG = Control group; CI = Confidence interval; IG = Intervention group; IUGR = Intrauterine growth restriction; NS = Not significant; OR = Odds ratio; RR = Risk ratio; SGA = Small for gestational age

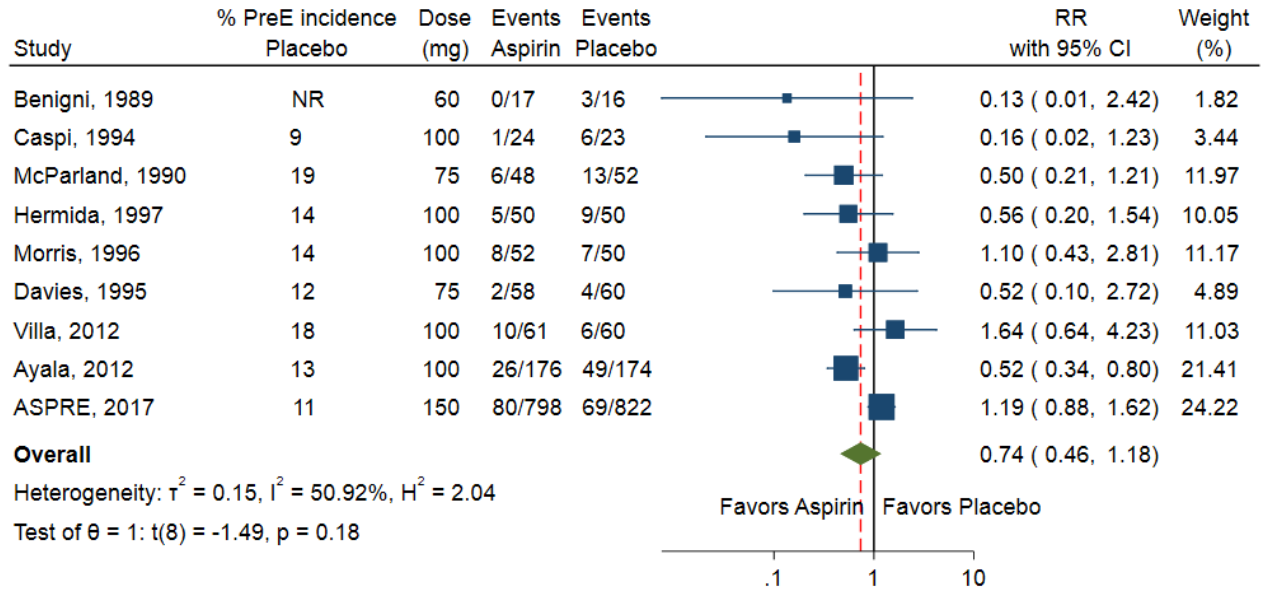
[*]The CLASP and MFMU trials reported relative risks and the ASPRE trial reported odds ratios.
[†]Statistical significance in this trial was set at <.01 for subgroup comparisons.
[‡]Comparison numbers calculated from main report, only percentages given
[§]Additional stratified comparisons reported in text, none statistically significant. We report in this table the comparisons discussed in our report.
[‖]Interaction test results not reported, but the authors reported in the text that there were no statistically significant subgroup differences. The study was underpowered, however, for comparing the small magnitude differences between groups.
[¶]Excludes participants with hypertension at baseline
[#]Study reported that p-values for effect estimates should be compared to 0.00625 to determine significance at the 5% level to adjust for multiple comparisons.

Appendix F Figure 1. Pooled Estimate of Mean Birthweight, Grams



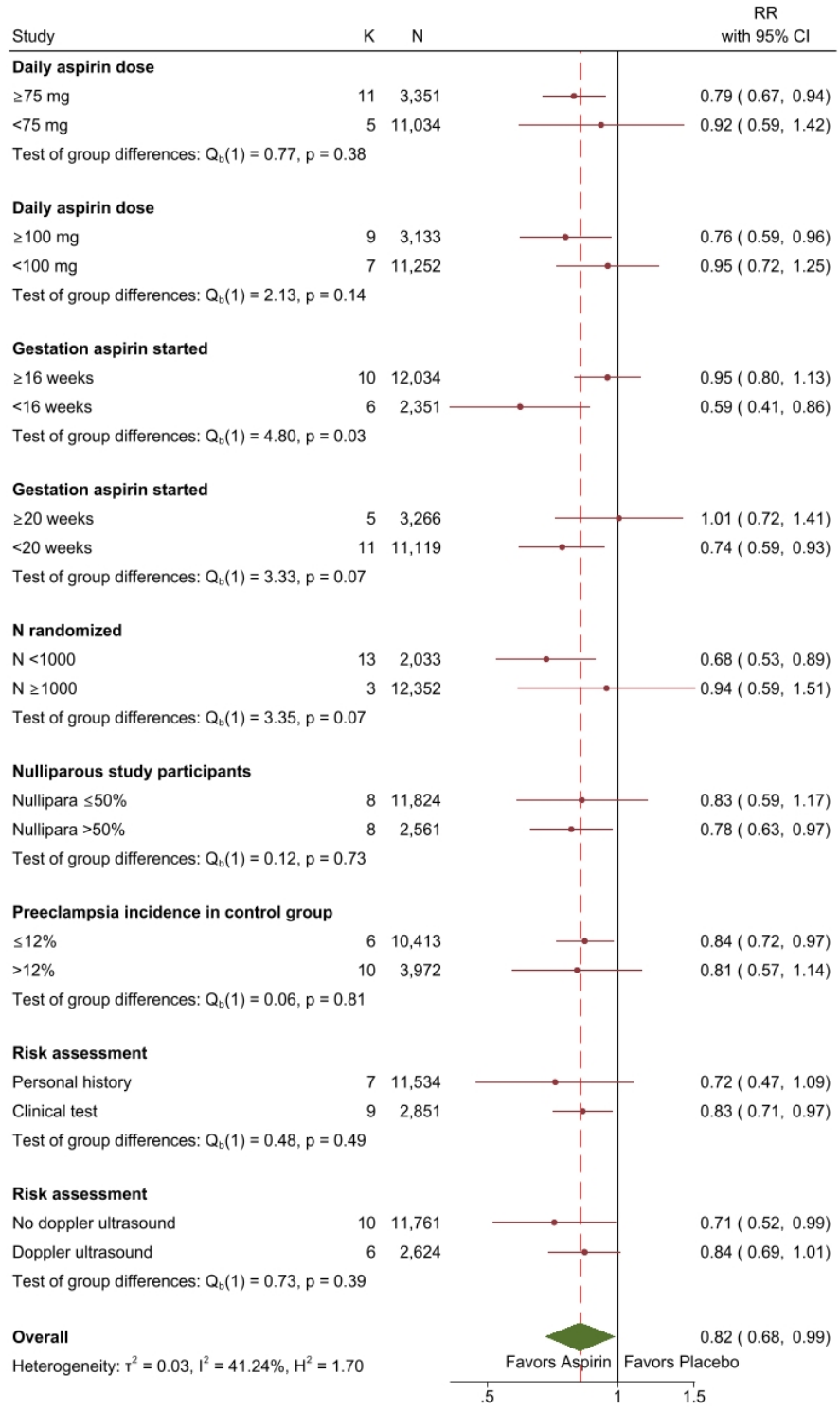
Abbreviations: CI = Confidence interval; mg = Milligrams; PreE = Preeclampsia; n = Sample size; NR = Not reported; SD = Standard deviation; WMD = Weighted mean difference

Appendix F Figure 2. Gestational Hypertension, Sorted by Study Size



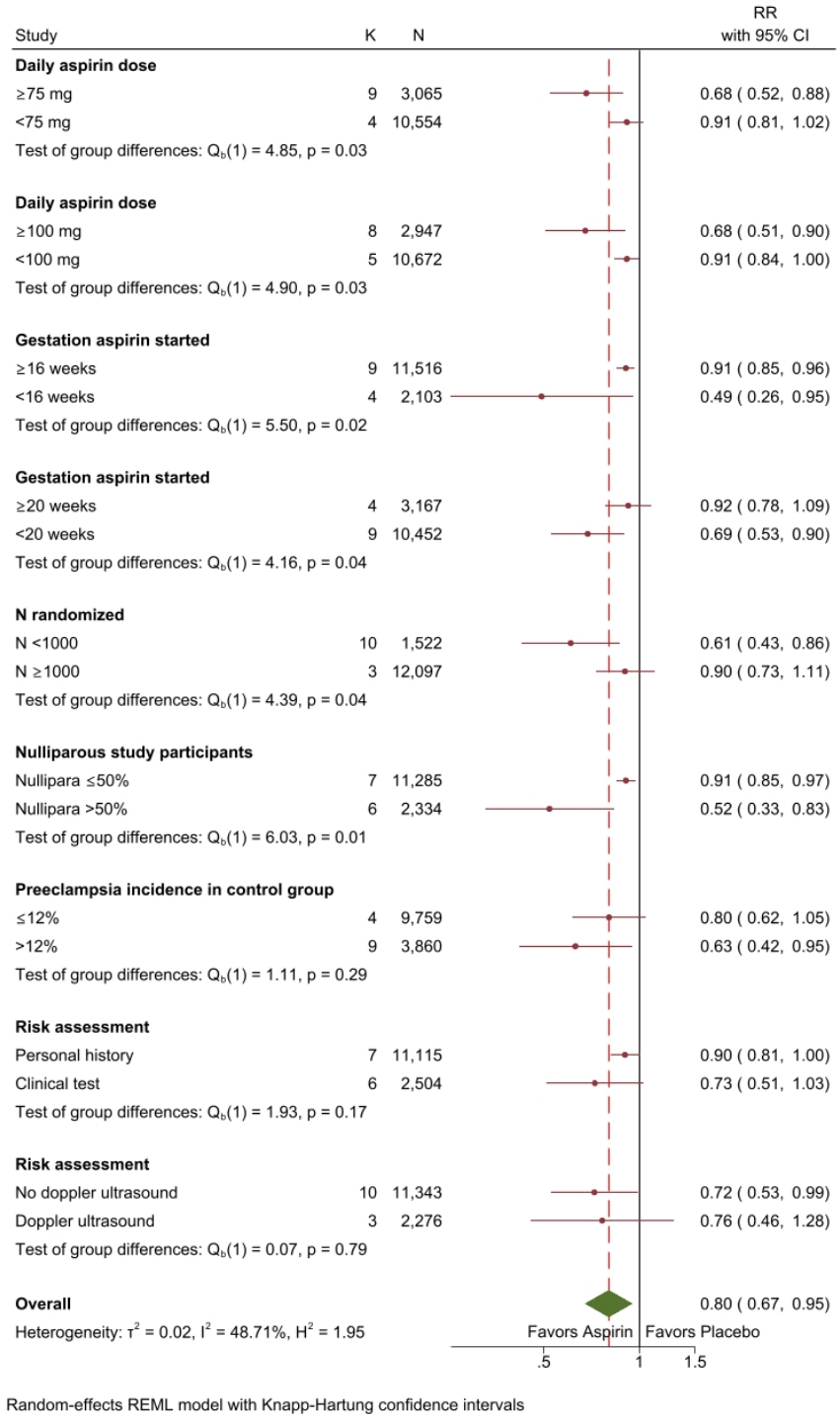
Abbreviations: CI = Confidence interval; mg = Milligrams; PreE = Preeclampsia; NR = Not reported; RR = Risk ratio

Appendix F Figure 3. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Small for Gestational Age or Intrauterine Growth Restriction



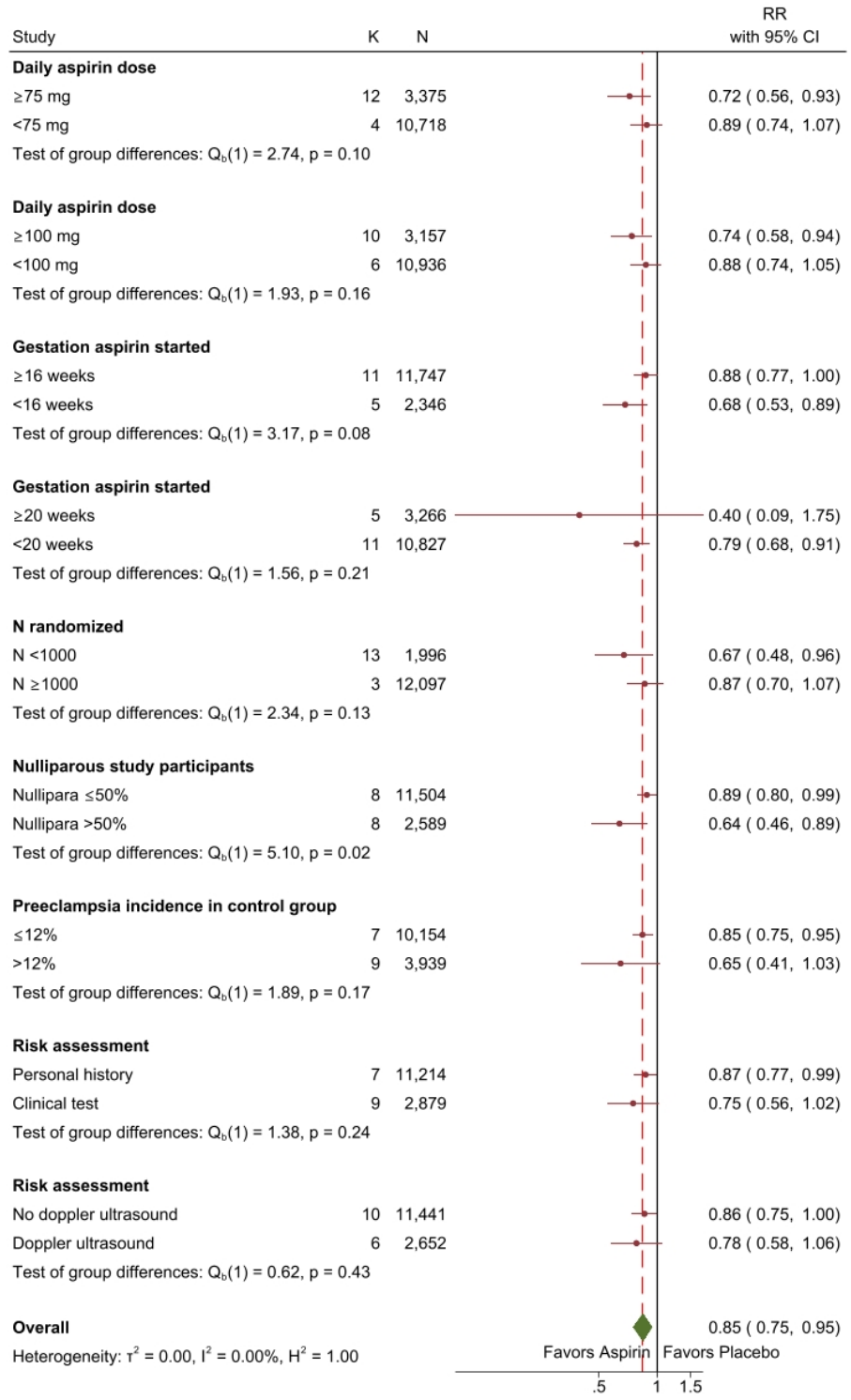
Abbreviations: CI = Confidence interval; K = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk

Appendix F Figure 4. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Preterm Delivery



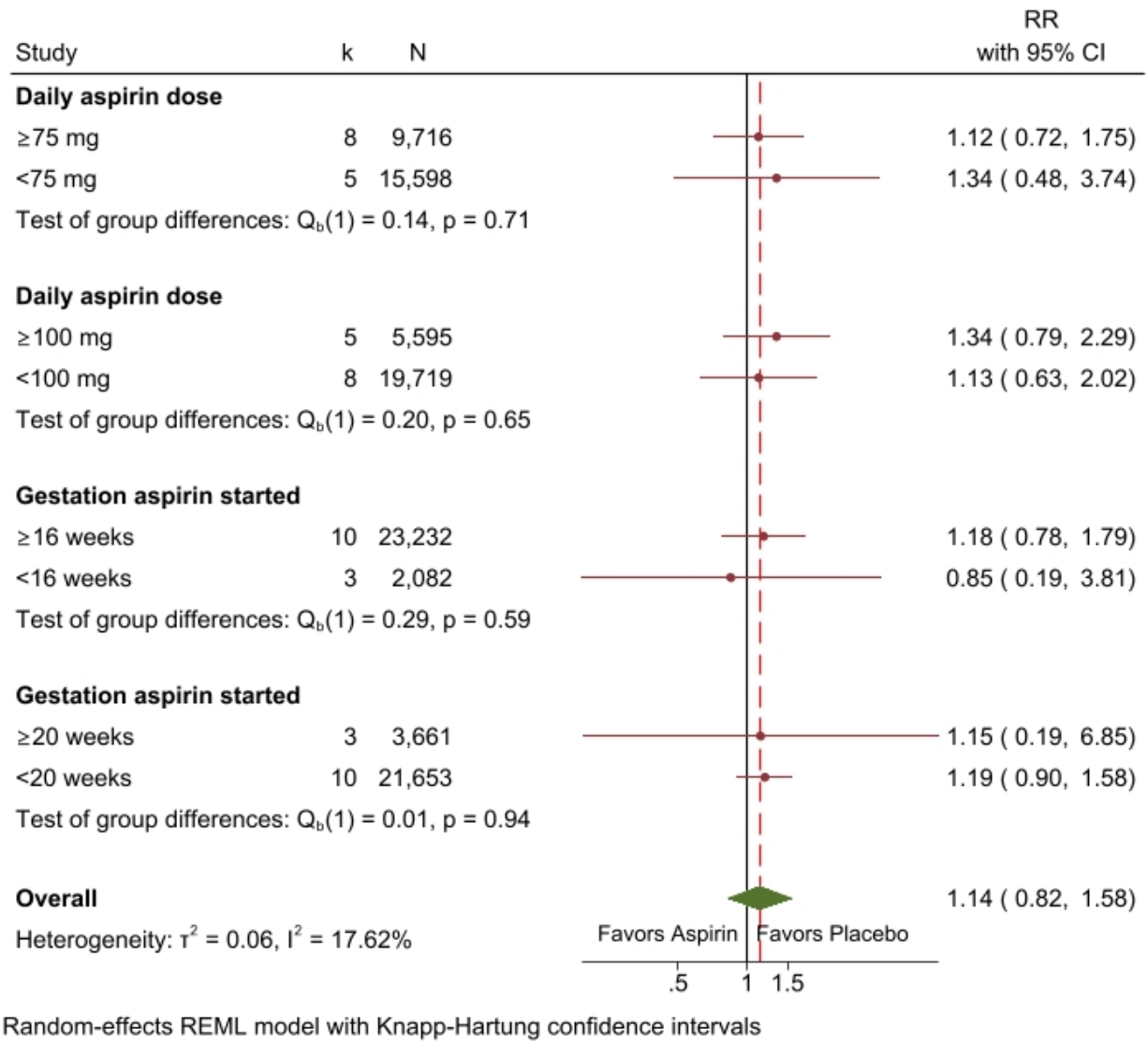
Abbreviations: CI = Confidence interval; K = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk

Appendix F Figure 5. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage, Timing, Study Design, and Population Characteristics on Preeclampsia



Abbreviations: CI = Confidence interval; K = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk

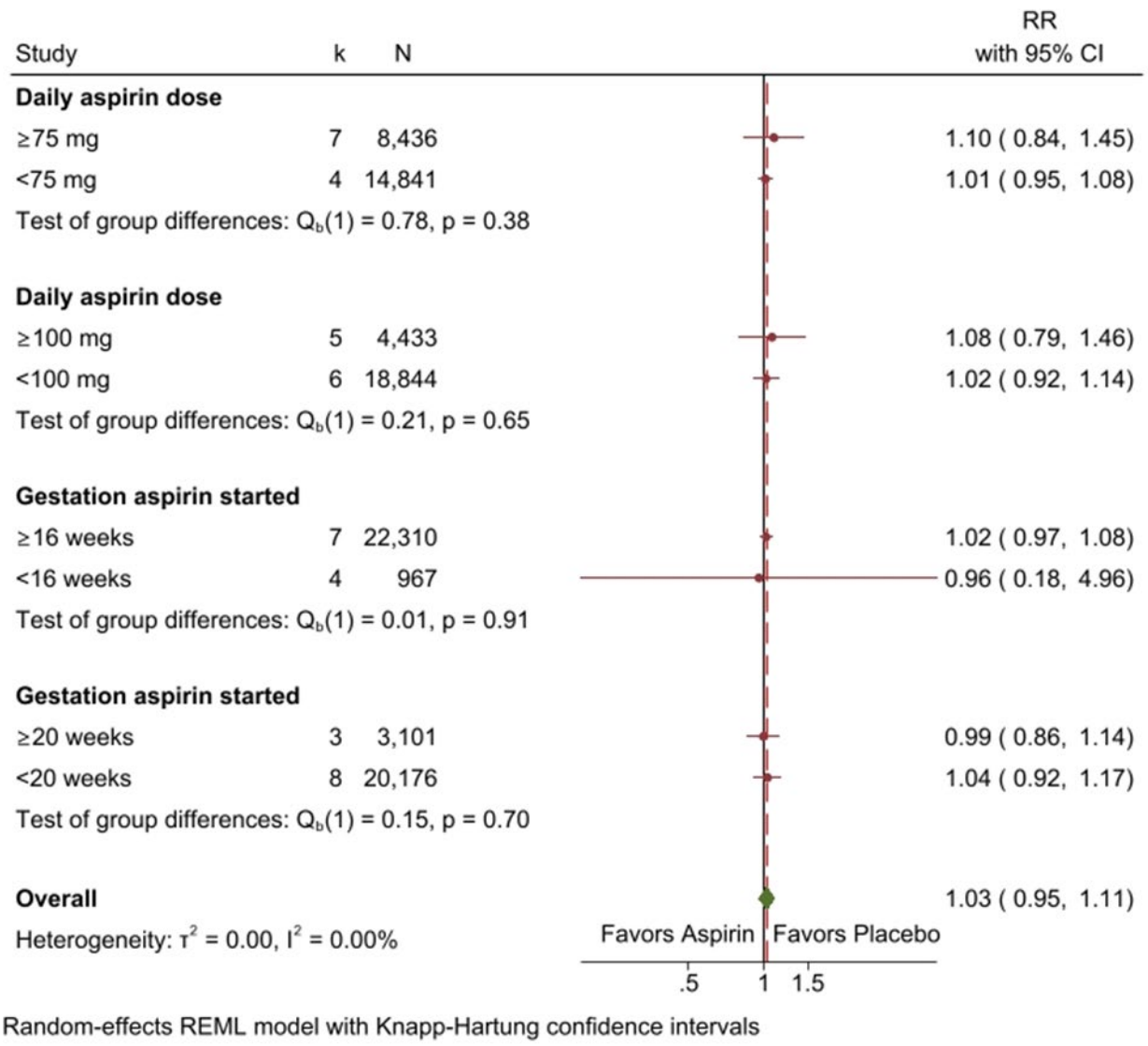
Appendix F Figure 6. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage and Timing on Placental Abruption*



Abbreviations: CI = Confidence interval; k = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk

*Excluded 3 studies with both groups having zero events

Appendix F Figure 7. Subgroup Analyses of Aspirin Effectiveness Comparisons for Dosage and Timing on Postpartum Hemorrhage*



Abbreviations: CI = Confidence interval; k = Number of studies; mg = milligrams; N = Number of observations; RR= Relative Risk

*Excluded 2 studies with both groups having zero events

Appendix G. Ongoing Studies

Trial identifier	Study name	Location	Estimated N and Age range	Interventions	Outcome Measures	Status
NCT03735433	The Effect of Two Aspirin Dosing Strategies for Obese Women at High Risk for Preeclampsia	USA	400 18-45 years	ASA, 81 mg vs. ASA, 162 mg	Incidence of Diagnosis of preeclampsia | Incidence of aspirin resistance based on incomplete inhibition of TBx2	Recruiting Start date: Jan 2019 Est completion date: Jan 2020
NCT03961360	Effectiveness of Higher Aspirin Dosing for Prevention of Preeclampsia in High Risk Obese Gravida (ASPREO)	USA	220 18-45 years	ASA, 181 mg vs. ASA, 162 mg	Preeclampsia diagnosis | Maternal Outcomes-Incidence of preterm preeclampsia | Maternal Outcomes-Gestational Hypertension | Maternal Outcomes-Placenta Abruption | Maternal Outcomes-Eclampsia | Maternal Outcomes-HELLP syndrome | Maternal Outcomes-Postpartum Hemorrhage | Maternal Outcomes-Other maternal bleeding | Maternal Outcomes-Need for blood transfusion | Neonatal Outcomes- Gestational age at delivery | Neonatal Outcomes-Delivery at < 37 weeks | Neonatal Outcomes-Apgar score at 5 min ≤ 5 | Neonatal Outcomes-Small for gestational age | Neonatal Outcomes-Neonatal Intensive Care Unit (NICU) length of stay | Neonatal Outcomes-Intraventricular Hemorrhage Grade III-IV | Neonatal Outcomes-Bronchopulmonary Dysplasia | Neonatal Outcomes-Necrotizing Enterocolitis	Recruiting Start date: May 2019 Est completion date: May 2020
NCT03893630	Role of ASpirin in Placental and Maternal Endothelial Cell Regulation IN Pre-eclampsia (ASPERIN)	USA	150 18-45 years	ASA, 81 mg vs. ASA, 162 mg vs. Standard of care	Change in Pulsatility Index (PI) | Onset of Pre-eclampsia | Severity of Pre-eclampsia | Composite Neonatal outcomes including frequency of Intraventricular hemorrhage (IVH), Bronchopulmonary dysplasia (BPD),	Recruiting Start date: April 2019 Est

Appendix G. Ongoing Studies

Trial identifier	Study name	Location	Estimated N and Age range	Interventions	Outcome Measures	Status
					Respiratory distress syndrome (RDS), Necrotizing enterocolitis(NEC) | Change in s-ICAM levels over time | Change in PIGF levels over time | Change in CRP levels over time | Change in IL-6 over time | Change in TNF over time	completion date: June 2020
NCT03574909	IRELAnD: Investigating the Role of Early Low-dose Aspirin in Diabetes (IRELAnD)	Ireland	300 18 years or older	ASA, 150 mg vs placebo	Preeclampsia | Birth weight | Preterm birth | Perinatal mortality | Parameters of neonatal morbidity: Gestational age at delivery | Parameters of neonatal morbidity: Birth weight | Parameters of neonatal morbidity: NICU admission | Respiratory morbidity: Duration of invasive ventilation | Duration of O2 | Duration of hospital stay | Use of nitric oxide | Number and type of inotropes | Duration of inotrope use | Apgar score | Umbilical artery acidosis at birth | Intracranial hemorrhage | Culture-proven sepsis | Necrotizing enterocolitis | Hypoxic ischemic encephalopathy | Shoulder dystocia | Composite measure of Maternal outcomes not directly related to primary outcome | Hemorrhage | Sepsis	Not yet recruiting Start date: Sept 2018 Est completion date: Sept 2021
NCT04158830	Aspirin (ASA) Therapy and Preeclampsia Prevention	USA	900 14-50 years	ASA, 81 mg vs. 2 x ASA, 81 mg	Preeclampsia	Not yet recruiting Start date: Dec 2019 Est completion date: Nov 2021
NCT04070573	Low Doses of Aspirin in the Prevention of Preeclampsia (ASAPP)	USA	400 18-60 years	ASA, 81 mg vs. ASA, 162 mg	Incidence of preterm (<37 weeks) preeclampsia | Incidence of preeclampsia with severe features |	Recruiting

Appendix G. Ongoing Studies

Trial identifier	Study name	Location	Estimated N and Age range	Interventions	Outcome Measures	Status
					Aspirin adherence | Maternal and Fetal Outcomes | Time-to-event for preeclampsia | Aspirin compliance | Impact of co-morbidities on incidence of preeclampsia	Start date: Oct 2019 Est completion date: Aug 2024