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Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment.

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Structured Abstract

Objective: We conducted a systematic review of the evidence on the use of low-dose aspirin for the prevention of morbidity and mortality from preeclampsia to support the U.S. Preventive Services Task Force (USPSTF) in updating its previous recommendation. Prior reviews have established that benefits of aspirin prophylaxis are not obtained in populations of healthy or unselected pregnant women not at high risk of preeclampsia. In this review we considered the evidence on benefits and harms of low-dose aspirin for women at elevated risk of developing preeclampsia and consequent maternal and fetal health outcomes. Three key questions (KQs) were systematically reviewed: 1) Is there evidence that aspirin reduces adverse maternal or fetal health outcomes? 2) Is there evidence that aspirin reduces incidence of preeclampsia? and 3) What are the harms of low-dose aspirin use during pregnancy?

Data Sources: We identified nine existing relevant systematic reviews and performed a search of MEDLINE, the Database of Abstracts of Reviews of Effects, PubMed, and the Cochrane Collaboration Registry of Controlled Trials for studies published from January 2006 through 2013. We supplemented searches by examining bibliographies from previous systematic reviews and retrieved articles, previous USPSTF reviews, and consulting outside experts. We searched Federal agency trial registries for ongoing and/or unpublished trials.

Study Selection: We conducted dual independent review of 525 abstracts against a priori inclusion and exclusion criteria. The 73 potentially relevant articles identified were then independently evaluated by two reviewers against the same inclusion/exclusion criteria and critically appraised for quality/risk of bias using USPSTF criteria. Discrepancies were resolved in discussion with a third reviewer. A single investigator extracted study characteristics and outcomes for all fair- to good-quality studies into tables and a second reviewer checked accuracy.

Data Analysis: Evidence for all KQs was qualitatively synthesized. Quantitative synthesis of outcomes where there was sufficient data used random-effects meta-analysis models as the primary analysis. Analyses were stratified by the timing of aspirin administration and dosage, with statistical tests of strata differences conducted. Funnel plots and tests for small-study effects were conducted.

Results: One large U.S. study (n=2,539), one large international study based in the United Kingdom (n=9,364), and 13 smaller trials were included for evaluation of benefits of aspirin. Additionally, six randomized, controlled trials (RCTs) of women not at increased risk for preeclampsia contributed to the analysis of harms. Five of these studies were prophylaxis RCTs of women with low or average preeclampsia risk: a good-quality multisite study in the United States (n=3,135) and a smaller U.S. study (n=606), a good-quality multisite study in France and Belgium (n=3,294), a good-quality hospital-based study in Barbados (n=3,647), and a fair-quality U.K.-based study (n=122). The sixth study was a good-quality Australia-based RCT of fetal growth restriction treatment (n=51). Two observational studies were also included for the review of harms: a good-quality cohort study following 47,400 women enrolled during pregnancy and a good-quality case-control study based on data from a large prospective cohort study (n=3,129).

(and perhaps 24%), with beneficial effects on perinatal health outcomes; intrauterine growth restriction (IUGR) was reduced 20 percent and preterm birth an estimated14 percent, although the actual effect for these two outcomes may be more modest, given the possible bias due to small-study effects. Consistent with findings of lower rates of preterm birth and IUGR, birth weight averaged 130 g more in infants whose mothers took low-dose aspirin. We did not find evidence of serious harms from aspirin use (i.e., no effect on perinatal mortality), although power was limited for such a rare event. Individual trials were inconsistent, with nonstatistically significant findings in the direction of both modest benefit and modest harm; pooling of perinatal mortality findings suggested a tendency toward a reduced (rather than increased) risk of perinatal mortality (relative risk [RR], 0.92 [95% CI, 0.76 to 1.96]), particularly when analyses were limited to only women at increased risk of preeclampsia (RR, 0.81 [95% CI, 0.65 to 1.01]). Similarly, available evidence on intracranial fetal bleeding suggested no effect with low-dose aspirin (RR, 0.84 [95% CI, 0.61 to 1.16]). Although there was no overall effect of low-dose aspirin on several maternal harms (i.e., postpartum hemorrhage, Cesarean delivery), we could not eliminate the possibility of an increased risk of abruption because of power limitations and heterogeneity of risk for preeclampsia. Pooling limited to trials enrolling higher-risk pregnant women (the target for aspirin intervention) somewhat attenuated the potential for harm from abruption, but results remained heterogeneous. Two observational studies on aspirin use during pregnancy had null findings for the potentially harmful outcomes considered (miscarriage and cryptorchidism).

Limitations: Very little new evidence has accrued since the completion of a number of large studies conducted in the 1990s. Since then there have been multiple systematic reviews, including one individual-level meta-analysis, and a few smaller trials (n<1,000). The serious health outcomes that are the aim of aspirin prophylaxis are rare and there is insufficient power, even in pooled analyses, to detect effects that could be clinically important.

There is evidence of small-study bias in the evidence we reviewed, based on funnel plots, formal statistical tests, and observation of forest plots sorted by sample size, showing a clear decrease in effect size with increasing sample size. Given that the large studies are from multiple sites, they likely share some of the features of small studies in terms of study operations. Those studies combined in the large multisite trials, however, are necessarily reported in the literature regardless of results, whereas null findings of small independent trials may be less likely to publish null results.

Trial characteristics cannot always be disentangled from study size due to the presence of small-study effects. The ability to draw conclusions related to dosage from the available trial evidence is limited by the fact that the two largest studies used 60 mg of aspirin, although they differed on other important characteristics. Thus, stratification by dosage is potentially confounded; the apparent benefit of a dose greater than 75 mg found in other systematic reviews could be due either to the small sample effect, a true dose effect, or a combination of these factors.

Conclusions: For women at elevated risk of preeclampsia, prophylaxis with low-dose aspirin (60 to 150 mg) beginning after the first trimester of pregnancy reduced risk of preeclampsia and important adverse perinatal health outcomes. Specifically, modestly reduced risks of preterm birth, IUGR, and possibly perinatal mortality were supported by the evidence. Consistent with

lower risk of preterm birth and IUGR, a significant difference in birth weight was also present. Statistical significance was not attained for the estimated 19 percent reduction in risk of perinatal mortality, although power to detect this difference was under 50 percent; there is a risk of incorrectly accepting a null result for perinatal mortality based on currently available data. The effects on perinatal mortality observed in the two largest trials were consistent with a benefit, although more modest.

The pooled results finding reduced risk of preeclampsia with low-dose aspirin supports the causal pathway leading to the observed direct health outcomes. The pooled results may have overestimated the benefit, however, given the evidence of small-study effects and more modest results in the two largest trials. However, given the consistency of the effect size in the large trials and the results of pooled analysis, at least a 10 percent reduction in preeclampsia was supported by the evidence. This reduction in preeclampsia incidence likely underlies the observed perinatal health benefits.

There was limited evidence of harms associated with low-dose aspirin use during pregnancy. A potential increased risk of abruption could not be ruled out, but evidence of harm from other bleeding-related complications, such as postpartum hemorrhage, maternal blood loss, and neonatal intracranial or intraventricular bleeding was not found. The evidence on longer-term outcomes for offspring from in utero aspirin exposure (low-dose) is very limited, but followup data from one large randomized, controlled trial is reassuring.

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CHAPTER 1. INTRODUCTION

Condition Definition

Preeclampsia is a multisystem inflammatory syndrome that is not well understood. It is defined as the onset of hypertension (blood pressure ≥140/90) and proteinuria during the second half of pregnancy (>20 weeks' gestation). While the condition can remain mild until delivery, it can also evolve rapidly into severe hypertension, proteinuria, and eclampsia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, with risk of organ and systemic complications and maternal or fetal death.[1,2] Even when preeclampsia does not proceed to HELLP syndrome or eclampsia, severe preeclampsia can lead to neurological and visual disturbances, epigastric or right upper quadrant pain, pulmonary edema, or cyanosis. The only curative treatment once preeclampsia develops is delivery, with obvious implications for the health of the infant when it occurs preterm.

Systems for diagnosing and classifying the severity of disease vary across professional societies and organizations, including the American College of Obstetrics and Gynecology (ACOG), the American Society of Hypertension (ASH), and obstetrics and gynecology professional organizations in the United Kingdom, Canada, New Zealand, and Australia. ACOG defines severe preeclampsia as any case of preeclampsia that includes one or more of the following characteristics: severe hypertension (systolic ≥160 mm Hg or diastolic ≥110 mm Hg), severe proteinuria (ACOG: >5 g/24 hours; ASH: >3g/24 hours), severe oliguria (very low urine output), cerebral or visual disturbances (i.e., headache, blurry vision, scotomata), right upper quadrant pain, pulmonary edema or cyanosis, impaired liver function, thrombocytopenia, or fetal growth restriction. Other organizations include the timing of onset (<35 weeks), nausea or vomiting, and chest pain or dyspnea among diagnostic criteria for severe preeclampsia. Severe preeclampsia can also be retrospectively diagnosed after the occurrence of major maternal or fetal morbidity.[3,4]

Other pregnancy-related hypertensive conditions overlap and can co-occur with preeclampsia. Chronic hypertension, for example, is defined as hypertension predating the pregnancy and/or continuing beyond 12 weeks postpartum. Women with chronic hypertension are diagnosed with superimposed preeclampsia if proteinuria develops after 20 weeks' gestation. Pregnant women who develop hypertension during pregnancy (without proteinuria) that subsides within 12 weeks postpartum are defined as having gestational hypertension. Women can also develop atypical preeclampsia, in which they have only proteinuria or hypertension coupled with systemic manifestations or preeclampsia occurs before 20 weeks' gestation or more than 48 hours postpartum.

Physicians have used the concept of early- and late-onset preeclampsia to define different manifestations of the syndrome. This concept also allows providers to distinguish between cases developing before 34 weeks' gestation (<35 weeks' gestation according to ASH) and those developing later.[3] This is important, as research has identified differences in the origins and outcomes of early-onset preeclampsia, which is thought to be related to aberrations in the placentation process.[3,5] Later-onset disease, on the other hand, is thought to be associated with maternal constitutional and environmental factors, such as multiple pregnancies, high body mass

index (BMI), comorbidities, and chronic hypertension. Early-onset preeclampsia is associated with more severe maternal and fetal outcomes.[3]

Prevalence

Approximately 2 to 8 percent of pregnancies are affected by preeclampsia, which is the second leading cause of maternal mortality worldwide.[6,7] In the United States, for example, 12 percent of maternal deaths are directly attributable to preeclampsia and eclampsia.[8] Complications of preeclampsia also contribute to approximately one in 10 pregnancy-related deaths attributed to anesthesia, cardiomyopathy, and placental abruption.[9] Serious morbidity, however, is far more common than mortality, and researchers have estimated that over one third of severe obstetric morbidities are related to preeclampsia.[10] While the prevalence of hospitalizations from severe preeclampsia/eclampsia rose from 9.4 to 12.4 per 1,000 deliveries in the United States between 1998 and 2006,[11] more recent data suggest that hospitalizations for eclampsia may be decreasing.[12] In addition to risks to the mother, preeclampsia also dramatically increases risks to the fetus or neonate, including intrauterine growth restriction (IUGR), small for gestational age (SGA), low birth weight, premature birth, oligohydramnios, placental abruption, low Apgar scores, neonatal intensive care unit admission, stillbirth, and neonatal death.[1] Because delivery is the only curative treatment, preeclampsia is a leading cause of iatrogenic preterm birth and low birth weight: 15 percent of U.S. preterm births are due to preeclampsia.[13] Infants born before term (<37 weeks of gestation) are at increased risk of morbidity and mortality, with risks rising dramatically with earlier delivery. Early-onset preeclampsia has the highest likelihood of becoming severe and is therefore more likely to require early preterm delivery.

A diagnosis of preeclampsia increases the need for obstetric intervention relative to pregnancies without preeclampsia to reduce maternal and/or fetal risks. Interventions include induction of labor (preterm or term), intravenous magnesium sulfate treatment, and emergency or planned cesarean delivery. While these interventions can have health-protective benefits for maternal health, they also incur maternal and neonatal health risks. Finally, there are also mental health burdens associated with preterm birth and negative birth outcomes.[14,15]

Disparities in Preeclampsia Risk and Prevalence

In the United States, the prevalence of preeclampsia and case-fatality rates reveal marked disparities. The greatest burden of preeclampsia is borne by nonHispanic black women. The rate of pregnancy-related death is four times greater in nonHispanic black women compared with nonHispanic white women, and death from preeclampsia is reported to be considerably higher in this population.[9,16] National data on chronic and gestational hypertension show that these conditions are more common in nonHispanic black women and are increasing over time, with an 87 percent increase reported from 1990 to 2009; these conditions appear to be least common in Asian and Pacific Islander and Hispanic women.[17] The increase in the rates of hypertensive conditions is especially troubling given that case-fatality rates from preeclampsia are three times higher in nonHispanic black women than whites, contributing to the large mortality disparity.[9]Approximately one third of the disparity in mortality from preeclampsia in black women stems from higher disease prevalence, but the higher case-fatality rates account for most

of the difference.[18] Disparities in risk factors for preeclampsia, such as chronic hypertension, diabetes, and high BMI, contribute to higher prevalence of preeclampsia in black women. Likewise, disparities in access to adequate prenatal care limit the opportunities to intervene before preeclampsia becomes more severe.[19] Indeed, inadequate prenatal care is associated with higher case fatality from preeclampsia for all women, likely due to the reduced opportunity for monitoring, detection, and early intervention.[9,16] Racial/ethnic disparities have also been observed, however, in a large study population (n=35,529) provided with early access to prenatal care. Minority women still experienced higher rates of preeclampsia than nonHispanic white women.[20] Finally, recurrent preeclampsia in subsequent pregnancies is more severe for black women than for white or Hispanic women.[21] Research is needed to assess whether low-dose aspirin could help to ameliorate this disparity in occurrence, severity, and fatality of preeclampsia in U.S. nonHispanic black women.

Pathophysiology and Natural History

The etiology and pathophysiology of preeclampsia are subjects of considerable research and ongoing theory development. Preeclampsia is generally understood to be an inflammatory condition that involves the process of placentation, but the underlying causes and precipitating factors and conditions for its development are not fully understood. Recent theory postulates that preeclampsia may develop through two different processes that can occur either alone or in combination. Early-onset preeclampsia, which tends to have more severe outcomes, may arise from aberrations in the process of placental development, whereby trophoblast cells fail to fully activate transformation of uterine spiral arteries (at approximately 12 to 16 weeks of pregnancy), resulting in placental ischemia. This relative ischemia and lowered placental perfusion cause the release of damaging factors (i.e., cellular debris, oxidized lipids, antiangiogenic factors, soluble endoglin) into the maternal bloodstream, resulting in inflammation and oxidative stress. Alternatively or additionally, preeclampsia may develop as a result of overactive inflammatory responses to normal placentation. Preexisting hypertension, diabetes, and other inflammatory conditions (e.g., lupus), as well as twin or higher order pregnancies, are thought to precipitate a systemic inflammatory response and oxidative stress process. Consistent with this theory of two processes, women with early-onset placental preeclampsia exhibit abnormal uterine artery ultrasound Doppler readings and placental morphology compared with women without preeclampsia or with later-onset disease.[2,3,22] Adding to this complexity, maternal and environmental factors may also contribute to the risk of developing preeclampsia involving problems with placental development. Thus, there is likely to be overlap between the two processes.

While we do not fully understand root causes of the placentation aberrations and inflammatory feedback loops that lead to preeclampsia, immune factors owing to the interaction of maternal physiology with fetal/paternal genes may play a role.[23] 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 a potential role of the immune system and paternal genetic influences.[1] Pursuit of definitive findings to explain patterns of disease risk, however, has not yet led to a comprehensive etiological understanding. Instead, the view that preeclampsia is a complex disease with multiple causes and interactions leading to its clinical

manifestation, as well as its intractability to effective treatment, make it an area of considerable scientific inquiry with important implications for women's health worldwide.

Significant maternal morbidities include cerebrovascular bleeding, retinal detachment, and complications from HELLP syndrome, such as major organ damage and failure.[3] Eclampsia occurs in approximately 1 to 2 percent of preeclampsia cases, with complications such as brain damage, aspiration pneumonia, pulmonary edema, placental abruption, disseminated coagulopathy, acute renal failure, cardiopulmonary arrest, and coma.[7]

While some studies have found evidence that preeclampsia may be a long-term risk factor for poor cardiovascular health,[24] common risk factors may explain this association. A recent study, for example, found elevated rates of cardiovascular mortality primarily in women with a history of preeclampsia, but the finding was found to be predominantly driven by those who had only one child.[25] This could indicate confounding with other health issues, since women with only one child may have had their child later in life, had fertility problems, or had severe pregnancy or delivery complications limiting future childbearing. Other studies have found elevated risk of poor cardiovascular health in the offspring of pregnancies affected by preeclampsia.[26] Whether or not preventing preeclampsia would benefit long-term cardiovascular health for women or their children is currently unknown. Notably, preeclampsia often remains mild and slowly progresses without any adverse health consequences for the mother or infant. Challenges in preventing and treating the disease are compounded by the difficulty of determining which patients will develop preeclampsia and go on to experience severe life-threatening complications. It has recently been suggested that preeclampsia may consist of multiple disease types with different causes, courses, and manifestations.[27] As understanding of the disease becomes more nuanced, the ability to assess individual risk and to develop targeted preventive strategies is likely to expand. Currently, however, tools for predicting and preventing preeclampsia are limited.

Risk Factors

There are no validated clinical tools or assays to predict early in pregnancy with sufficient sensitivity and specificity who will develop preeclampsia or experience adverse outcomes. Systematic review evidence for uterine artery Doppler ultrasound readings in the second trimester, particularly increased pulsatility index and bilateral notching, have reasonable test performance characteristics for identifying low- and high-risk women who will develop severe preeclampsia.[28] However, when undertaken in the first trimester, the readings have only low to moderate predictive sensitivity and specificity. Reviews and test performance studies of existing and candidate biomarkers and clinical tests do not yet support their use in routine clinical care to identify women at increased risk of preeclampsia.[29-31]

The most consistent risk factors resulting in the highest preeclampsia incidence based on patient medical history are previous preeclampsia, certain chronic medical conditions (e.g., diabetes, chronic hypertension, renal disease, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome), and multifetal pregnancy.[32] Moderately increased risk for preeclampsia is associated with first birth, older maternal age (i.e, ≥35 years), high BMI (≥35 kg/m^2), family history of preeclampsia (mother, sister), and other personal

history risk factors (e.g., pregnancy interval over 10 years, low birth weight).[33] Risk factors with less consistent evidence that are the subject of ongoing research include changes in paternity between pregnancies, reduced exposure to paternal semen (in vitro fertilization, sperm donation), interpregnancy weight change,[34] history of migraine headaches, and various biomarkers and clinical readings.[1,35,36]

Efforts to develop predictive models for identifying women who will develop preeclampsia and its adverse consequences have been undertaken, but are not yet sufficient.[37,38] Multiple risk factors can heighten preeclampsia risk, and efforts to develop and validate multivariable algorithms for risk prediction are ongoing.[39,40]

Interventions to Prevent and Treat Preeclampsia

Efforts to identify and evaluate interventions that would prevent or delay the onset of preeclampsia have included studies of diet, weight loss, activity level, vitamins, antioxidants, nitrates, and various candidate anticoagulant and antiplatelet medications, such as heparin, low-dose aspirin, and dipyridamole, either alone or in combination. While a few of these have shown benefit in initial studies, the most consistent and promising prophylaxis, showing modest benefit in rigorous randomized trials, has been low-dose aspirin.

Once preeclampsia develops, delivery of the placenta is the only treatment. Upon delivery, blood pressure and laboratory readings generally return to normal-range values within a few days, although some women experience persistent high blood pressure that usually resolves within 6 weeks.[13] For women who develop severe preeclampsia, intravenous administration of magnesium sulfate is effective for reducing the risk of eclamptic seizures. Depending on the timing of the onset of preeclampsia, clinical decisions regarding expectant management or induction of labor are required, especially for preterm preeclampsia (<34 weeks); while continuation of pregnancy could confer improvements in neonatal outcomes, it risks stillbirth and maternal harm.

Current Clinical Practice

The clinical application of low-dose aspirin to prevent the development of preeclampsia has increased over the past decade, as evidence suggesting its potential effectiveness has accrued. A 2010 analysis to investigate the clinical variation in therapeutic treatments for preeclampsia conducted in the United Kingdom found that 24 percent of pregnant women at high risk for developing preeclampsia had been prescribed low-dose aspirin (75 mg/day).[41] Similarly, a survey of German obstetricians (n=717) found that 38.1 percent reported prescribing aspirin to patients with moderate or severe hypertension during pregnancy.[42] A survey of South African obstetricians (n=432) that investigated the clinical management of hypertensive disorders in pregnancy found that 58 percent would prescribe low-dose aspirin to prevent preeclampsia in their patients.[43] A study of Swedish obstetricians (n=92) reported that 8 percent would prescribe low-dose aspirin to patients with mild hypertension and 20 percent would prescribe aspirin to patients with severe hypertension.[44] These international data demonstrate that, while

obstetricians have begun to prescribe aspirin to their patients who are at risk of developing preeclampsia, clinical practice still varies considerably. Data on preeclampsia prevention practices using low-dose aspirin by U.S. physicians are not available.

In 2009, the National Institute for Health and Clinical Excellence (NICE) released evidence-based guidance for managing hypertensive disorders during pregnancy.[45] It recommended that women at high risk for developing preeclampsia (women with a history of hypertensive disease in a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or 2 diabetes, or chronic hypertension) take 75 mg of aspirin a day starting at 12 weeks until the baby is born (**Table 1**). Similarly, it recommends that women with more than one moderate risk factor (first pregnancy, age ≥40 years, pregnancy interval of >10 years, BMI ≥35 kg/m^2, family history of preeclampsia, or multiple pregnancies) take 75 mg of aspirin per day starting at 12 weeks' gestation and continuing until the baby is born.[45]

In 2011, the World Health Organization (WHO) issued "Recommendations for Prevention and Treatment of Preeclampsia and Eclampsia," which comprised 23 recommendations.[46] Among these recommendations is use of low-dose aspirin (75 mg/day) by women deemed high-risk and initiation early during pregnancy (<20 weeks and as early as 12 weeks). In this review, WHO defined women as being at high risk of preeclampsia if they had any of the following in their health history: previous preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multiple pregnancies.[46] In its recommendation, WHO cautioned that, while using low-dose aspirin appears to be beneficial for women who are at high risk of developing preeclampsia, there is a scarcity of evidence to suggest that further subgroups of high-risk women could benefit from aspirin therapy. The evidence used to support the recommendation was heavily based on a 2007 Cochrane review[47] of 59 randomized controlled trials (RCTs) conducted in women considered to be at moderate or high risk of developing preeclampsia. This Cochrane review found a significant risk reduction in women who received any antiplatelet agent compared with women who received placebo or no treatment (relative risk [RR], 0.82 [95% CI, 0.78 to 0.89]). While this finding was apparent regardless of risk stratification, it was more pronounced in women deemed high risk (RR, 0.75 [95% CI, 0.66 to 0.85]). This review also investigated the role of aspirin dosage and found that increased risk reduction for developing preeclampsia was apparent with low-dose aspirin of 75 to 150 mg/day, but not in trials using less than 75 mg/day.[46]

Previous USPSTF Recommendation

In 1996, the U.S. Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to recommend for or against the routine use of aspirin for the prevention of either preeclampsia or IUGR. The USPSTF found inadequate evidence that aspirin confers benefits to pregnant women at increased risk of preeclampsia. Benefits to infants of these mothers were suggested by significant reduction in preterm birth, but a lack of consistency in the inclusion criteria of studies and a lack of other health benefits in infants led to an overall assessment that evidence on benefits remained inadequate. Aspirin use had also been associated with risk of placental abruption in one included study. Therefore, the USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of aspirin prophylaxis to prevent preeclampsia in pregnant women at increased risk of preeclampsia.

CHAPTER 2. METHODS

Scope and Purpose

This systematic review provides updated evidence regarding the effectiveness of aspirin in preventing preeclampsia in women at increased risk for developing the condition, reducing adverse health outcomes in women at increased risk for preeclampsia, and assessing the harms of aspirin use during pregnancy. The USPSTF will use this review to update its 1996 recommendation on the prophylactic use of aspirin to prevent preeclampsia in pregnancy. This review includes all trials from the previous review that met current inclusion/exclusion criteria as well as more recently published studies.

Key Questions and Analytic Framework

Following the methods of the USPSTF,[48] we developed an Analytic Framework (**Figure 1**) and Key Questions (KQs) to guide the literature search, data abstraction, and evidence synthesis for this topic. The KQs are:

1. Is there evidence that aspirin reduces adverse maternal or perinatal health outcomes in women at increased risk for preeclampsia?
2. Is there evidence that aspirin prevents preeclampsia in women at increased risk for preeclampsia?
3. What are the harms of aspirin use during pregnancy?

Data Sources and Searches

In addition to considering all studies from the previous review for inclusion, we identified one good-quality patient-level meta-analysis published in 2007[49] and one 2007 systematic Cochrane review[47] that we used as source documents for studies to evaluate against our inclusion criteria. Additionally, we performed a comprehensive search of MEDLINE, PubMed, Database of Abstracts of Reviews of Effects, and the Cochrane Collaboration Registry of Controlled Trials for studies published between January 2006 and January 1, 2013. We worked with a medical librarian to develop our search strategy (**Appendix A**). All searches were limited to articles published in the English language. The literature search results were managed using version 12.0 of Reference Manager® (Thomson Reuters, New York, NY), a bibliographic management software database.

To ensure the comprehensiveness of our retrieval strategy, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify relevant articles that were published outside the search timeframe or not identified in our literature searches. In addition, we obtained references from outside experts. We also searched Federal agency trial registries and WHO's International Clinical Trials Registry Platform for ongoing and/or unpublished trials (**Appendix B**) and used news and table-of-contents alerts from Google

(Google, Inc., Mountain View, CA) and ScienceDirect (Elsevier, Maryland Heights, MO) to help identify potentially eligible trials that were published during the period between bridge searches.

Study Selection

Two reviewers independently reviewed the title and abstracts against inclusion and exclusion criteria for design, population, intervention, and outcomes (**Appendix A**). Two reviewers then independently evaluated the full-text article(s) of all potentially included studies against the complete inclusion and exclusion criteria. Disagreements in 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 C**.

We developed an a priori set of criteria for inclusion and exclusion of studies based on our understanding of the literature (**Appendix A Table 1**). For KQs 1 and 2, examining the effectiveness of aspirin in preventing preeclampsia and/or adverse health outcomes, we included only RCTs of pregnant women at an elevated risk of preeclampsia based on patient characteristics and medical history. We did not specify risk criteria required for identifying participants in included studies, but included any study that employed a risk-selection approach aimed at achieving a study population with high preeclampsia prevalence. This could include a combination of risk factors based on medical history and/or clinical measurements known to be associated with the risk of preeclampsia, or in the case of pragmatic trials, the clinician's judgment of preeclampsia risk. Regarding nulliparity as a risk factor, preeclampsia occurs more often in first births than in subsequent births, but incidence rates are relatively low for nulliparous pregnant women (2% to 4%). Given modest to null benefits observed in prior trials of aspirin for nulliparous women and low pragmatism of assigning treatment to all, studies with nulliparity as the sole risk factor were not included in the evaluation of benefits of aspirin prophylaxis (KQs 1 and 2).

For KQ 3, examining the harms of aspirin use during pregnancy, we were more inclusive and considered RCTs and nonrandomized observational studies of pregnant women (healthy, nulliparous, or at increased preeclampsia risk), as well as fetuses or infants. We made this decision based on our view that the level of preeclampsia risk would not modify harms as it does benefits. In addition, we used broader inclusion criteria for harms because we did not want to restrict the opportunity to identify rare or unusual harms that could occur with aspirin use during pregnancy. For all KQs, we were interested in interventions that compared patients receiving 50 to 150 mg of aspirin with a placebo or "no treatment" group. This is a deviation from the 2008 review, which excluded "no treatment" groups. We included "no treatment" studies in the current review because there is good evidence of a pathophysiologic element in these intervention and we did not want to exclude potentially important evidence. However, to ensure that any effects observed were the result of the aspirin intervention and not some other factor, we excluded studies with interventions with nonaspirin antiplatelet medications or aspirin combined with another potentially active substance. We limited our included studies to those that were deemed good or fair quality by the USPSTF quality rating standards.[50] We excluded poor-quality studies and those not published in English. In addition, we considered only studies set in countries defined by the Human Development Index as "very high human development" (>0.90).

Reviewed outcomes are fully listed in **Appendix A Table 1**.

Quality Assessment of Evidence

Two reviewers independently assessed the methodological quality of each study using predefined criteria developed by the USPSTF[48] and supplemented with NICE methodology checklists for observational studies.[51] Discordant quality ratings were resolved by discussion and consultation with a third reviewer, if necessary. We assigned each study a final quality rating of good, fair, or poor.

Good-quality RCTs had adequate randomization procedures and allocation concealment, blinded outcome assessment, reliable outcome measures, similar groups at baseline (i.e., little to no statistically significant differences between groups in baseline demographics and characteristics), and low attrition (≥90% of participants had followup data, with <10 percentage-point difference in loss to followup between groups). These trials used conservative data-substitution methods if missing data were inferred. Trials were downgraded to fair if they were unable to meet the majority of the good-quality criteria. Trials were rated as poor quality if attrition was greater than 40 percent or differed between groups by 20 percentage points. We also rated trials as poor quality if there were any other "fatal" flaws that seriously affected internal validity. We excluded poor-quality studies from this review (**Appendix A Table 2** and **Appendix C**).

Good-quality observational studies exhibited unbiased selection of the nonexposed cohort and ascertainment of exposure preceding the outcome, and were conducted in populations without the outcome of interest at the beginning of the study. Further, these studies had reliable outcome measures, blinded assessment, low attrition, adjustment for potential confounders, and no other important threats to internal validity. Observational studies were downgraded to fair quality if they were unable to meet the majority of good-quality criteria. Poor-quality observational studies had multiple threats to internal validity and were excluded from the review.

Data Extraction

One reviewer extracted data from all included studies rated as fair or good quality into a standard evidence table and a second reviewer checked the data for accuracy. Elements abstracted included population characteristics (e.g., baseline demographics, BMI, concurrent conditions, family or prior history of preeclampsia, smoking status), study design (e.g., recruitment procedures, inclusion/exclusion criteria, followup, and population adherence), intervention characteristics, and health outcomes of both the mother and fetus.

Health outcomes included the number of participants experiencing an event and incidence rates where appropriate. For KQ 1 (efficacy of aspirin in reducing adverse maternal and fetal/neonatal health outcomes), we abstracted the following maternal health outcomes when reported: organ/system injury or failures (e.g., HELLP syndrome), Cesarean delivery, and maternal mortality. In addition, we abstracted the following fetal health outcomes when reported: preterm birth (defined as birth before 37 weeks); gestational age; birth weight; IUGR/SGA; potential

complications from Cesarean delivery, labor induction, or eclampsia prophylaxis (e.g., low Apgar score); and perinatal mortality. For KQ 2 (efficacy of aspirin in preventing preeclampsia), we abstracted the incidence of preeclampsia reported in each RCT. For KQ 3 (harms of aspirin use in pregnancy), 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

We created summary evidence tables for each of the main outcomes or sets of outcomes (i.e., preeclampsia incidence, maternal health outcomes, fetal health outcomes, and adverse events), along with important population characteristics and study design features. These tables were the basis of our qualitative synthesis, where we identified the range of results and looked for possible associations between study results and population or study characteristics.

In addition, we conducted meta-analyses to estimate the pooled effect size of each main outcome that was reported in at least one third of the trials for the relevant KQ (results shown in **Figures 2–10**). Additional forest plots showing key stratifications and sensitivity analyses are available in **Appendix E Figures 1–15**.

We used the metan procedure in Stata 11.2 (StataCorp, LP, College Station, TX) for all meta-analyses.[52] For the outcome of birth weight we entered the mean birth weight in grams for each group and the associated standard deviations (SDs) to estimate the pooled weighted mean difference between groups. For dichotomous outcomes, we entered the number of events and nonevents and estimated risk ratios using the DerSimonian and Laird method for all outcomes except those in which less than 10 percent of participants experienced the event.[53] The random-effects model is appropriate for the body of evidence we reviewed, because we do not assume that there is one true effect size, but rather a range of effect sizes that might be obtained depending on the diverse study characteristics and populations. For pooled analysis of rare events, we used a fixed-effects Mantel-Haenzel model or, if events were extremely rare (<1%), the Peto odds ratio to avoid bias associated with rare events.[54] We also included prediction intervals in our forest plots, which provide a 95 percent estimate of where newly conducted trials would fall, assuming the between-study variability in the included trials held for new trials.[55] The prediction intervals are shown on the forest plots by the horizontal lines that extend out from the diamond showing the 95 percent CI of the pooled effect.

We examined the I^2 statistic as a measure of statistical heterogeneity. We applied the Cochrane Collaboration's rules of thumb for interpreting heterogeneity: less than 40 percent likely represents unimportant heterogeneity, 30 to 65 percent represents moderate heterogeneity, 50 to 90 percent represents substantial heterogeneity, and greater than 75 percent indicates considerable heterogeneity among the studies.[56] In addition, we used funnel plots to examine small-study effects (possible indication of publication bias) and ran the Egger's test and, for dichotomous outcomes, Begg's test, to assess statistical significance of imbalance in study size and findings that would indicate a pattern. Funnel plots visually display the relationship between study size and effect size and direction. A funnel plot with few or no studies in the lower right

quadrant indicates the absence of small studies from the body of published evidence. We also sorted forest plots by number of study participants to visually evaluate trends in effect sizes by study size. While small-study effects can arise from different causes, they often occur when small studies showing null or negative findings are left unpublished. This bias can result in an overestimation of the benefit of treatment and should be taken into account when interpreting meta-analyses.

We sought to recognize patterns in the study results using visual examination of forest plots sorted and stratified by potentially important prespecified study characteristics. Specifically, we examined the approach to preeclampsia risk status identification, aspirin dosage, timing of aspirin initiation, and study sample size according to a priori analytic plans. In addition, we conducted post hoc forest plot analyses to assess potential patterns in the year of publication, duration of aspirin treatment, and control group preeclampsia rate to identify potential associations with heterogeneity of treatment effects across studies. For a priori analyses, statistical tests of effect-size differences between strata were conducted to assess apparent differences in effect size by dosage (≤75 vs. >75 mg), timing of treatment initiation (<16 weeks' vs. ≥16 weeks' gestation), and whether a clinical test had been used to determine preeclampsia risk versus patient medical history or pregnancy characteristics. In addition, we stratified the analysis of harms by whether the studies were of women at elevated preeclampsia risk or low to average risk.

We conducted two sets of sensitivity analyses. In the first, we explored the effects of removing from the pooled analysis a trial with inconsistent findings and a protocol that differed substantively from the others.[57] In the second, we explored the effects of dropping participants entered into the largest trial (Collaborative Low-dose Aspirin in Pregnancy [CLASP]) for the sole reason of elevated IUGR risk, leaving in the pooled analysis only women enrolled in trials based on their elevated preeclampsia risk.[58] This sensitivity analysis was motivated by the observation that the smoking rate was very high in the IUGR-only risk group, and that prior IUGR from smoking, or current smoking, may have been the motivating risk factors for their selection for the trial. Our review aims to isolate the effect of aspirin prophylaxis on prevention in women at elevated risk of preeclampsia, and these study participants were not entered into the trial for preeclampsia prevention. Results of sensitivity analyses are discussed, but all study participants are included in pooled risk estimates.

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)*baseline risk). Because there was a wide range of baseline risk for some of the outcomes (preeclampsia, IUGR, preterm birth), we chose baseline risk levels empirically using the included studies and roughly corresponding to the 20th, 50th, and 80th percentiles of risk. For abruption, we estimated the NNT separately for women known to be at risk of preeclampsia and for general- or low-risk women, using two levels of risk for each group based on the high and low values from included studies that had at least one event in the control group. From the absolute risk reduction for every level of baseline risk tested, NNT was calculated as the inverse of the absolute risk ratio.[56]

USPSTF Involvement

This research was funded by AHRQ under a contract to support the work of the USPSTF. The authors worked with three USPSTF liaisons at key points throughout the review process to develop and refine the scope, Analytic Framework, and KQs; to resolve issues around the review process; and to finalize the evidence synthesis. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the draft evidence synthesis, and distributed the initial evidence report for external review by outside experts, including representatives of professional societies and Federal agencies. The final published systematic evidence review was revised based on comments from these external reviewers.

CHAPTER 3. RESULTS

Literature Search

Our literature search yielded 525 unique citations. From these, we reviewed the full text of 73 articles (**Appendix A Figure 1**). Of these, 23 studies (27 articles) met our inclusion criteria. We excluded the remaining 46 full-text articles (**Appendix C**).

We identified 15 studies (eight good-quality) that met inclusion criteria for KQ 1 (maternal and perinatal health), 13 studies (eight good-quality) that met inclusion criteria for KQ 2 (preeclampsia), and 21 studies (14 good-quality) that met criteria for KQ 3 (maternal, perinatal, and developmental harms). For KQs 1 and 2, we included only RCT studies of women at elevated risk of preeclampsia. For KQ 3, on the other hand, we also considered studies of healthy pregnant women. All included RCTs were placebo controlled. Details of study design and baseline demographics for each study are provided in **Appendixes D** and **E**.

Overall Summary of Results (KQs 1 to 3)

We included one large U.S. trial[57] (n=2,539), one large international trial coordinated from the United Kingdom[58] (n=9,364), and 13 smaller trials from various countries[59-71] to evaluate the benefits of aspirin on preeclampsia. Additionally, we included six RCTs of women not at increased risk for preeclampsia for KQ 3 (harms). These six RCTs included a good-quality multisite study conducted in the United States[72] (n=3,135), a smaller U.S. study[73] (n=606), a good-quality multisite study in France and Belgium[74] (n=3,294), a good-quality hospital-based study in Barbados[75] (n=3,647), a fair-quality U.K.-based study[76] (n=122), and a small good-quality Australia-based RCT of fetal growth restriction treatment[79] (n=51). We also included two observational studies, one in the United States and one in Denmark, for KQ 3 (harms). These studies were a good-quality cohort study[77] that included 47,400 women enrolled during pregnancy and a good-quality case-control study[78] that used data from a large prospective cohort study (n=3,129).

Trials included to assess benefits initiated aspirin treatment at a range of gestational time periods and used a variety of aspirin dosages (**Appendix D Table 1**). All included trials initiated aspirin treatment after the first trimester and often reported a range of weeks in which initiation occurred (e.g., 12 to 16 weeks' gestation). The most common treatment discontinuation date was delivery, but six trials[57,62,66,69,71,74] stopped aspirin treatment before delivery, as early as 35 weeks[69] or at the point when preeclampsia developed.[57] Aspirin dosages ranged from 60 to 150 mg daily, with one trial reporting a dosage of 0.5 mg/kg daily (based on the average reported weight at baseline, the dose was calculated to be 49 mg daily).[67] The majority of trials used either dosages of 60 mg (six trials[58,60,70,72,73]) or 100 mg (eight trials[59,61-64,66,69,74]).

Baseline characteristics and risk factors of included trials were often sparsely reported (**Appendix D Table 2**). Overall, the population of women included in the trials was young (mean age, 20.3 to 31 years) and predominantly white (assumed from trial country of origin and

approximately 49% to 73%), which is important to consider given the reported increased risk of preeclampsia in black women. Nulliparity is an established moderate risk factor for preeclampsia; when reported, the number of women who were nulliparous ranged from 28 to 100 percent. A history of smoking and current smoking during pregnancy was reported in 10 trials[57,58,65,70-72,74,76,79] and ranged from approximately 10 to 40 percent.

Only nine of the 23 studies included in this review reported any race/ethnicity data (**Appendix G**).[57,62,65,66,71-73,76,78] Of these nine studies, all RCTs, except for one case-control study, reported the baseline comparability of the treatment groups by race/ethnicity.[71-73] One trial reported the racial/ethnic composition (whites compared with nonwhites) of the four high-risk groups enrolled (i.e., diabetes, hypertension, multifetal gestation, previous preeclampsia).[57] In that trial, there were considerable differences in the racial and ethnic composition of the risk groups. For example, 71 percent of study subjects with prior preeclampsia were black compared with only 39 percent in the diabetes group. Stratified risk results were reported in the text only for preeclampsia. Aspirin was ineffective for preventing preeclampsia in all four risk groups, regardless of race.

Based on pooled results, low-dose aspirin administered after the first trimester of pregnancy to women at elevated risk of preeclampsia modestly reduced the risk of preeclampsia and associated perinatal health outcomes (i.e., IUGR, preterm birth). Available evidence suggests that this reduction is at least a 10 percent risk reduction in preeclampsia (and perhaps a 24% reduction) (**Figure 2**). A meta-analysis revealed a 14 and 20 percent reduced risk of preterm birth and IUGR, respectively (**Figures 3** and **4**). The actual effect may be more modest, however, given the possible bias due to small-study effects. Consistent with findings of reduced preterm birth and IUGR, birth weight averaged 130 g more in infants whose mothers took low-dose aspirin. We did not find evidence of serious harms from aspirin use (i.e., no effect on perinatal mortality), although power was limited for such a rare event; individual trials were inconsistent, with nonstatistically significant findings in the direction of either modest benefit or harm. Pooling suggested a trend toward reduced (rather than increased) risk of perinatal mortality (RR, 0.92 [95% CI, 0.76 to 1.11]), with a tendency toward further reduced risk when pooling was limited to women at elevated risk for preeclampsia (**Figure 5**). Similarly, although more sparsely reported, available evidence suggested no effect of intracranial fetal bleeding with low-dose aspirin (RR, 0.84 [95% CI, 0.61 to 1.16]) (**Figure 6**). Although there was no overall effect of low-dose aspirin on other possible maternal harms (i.e., postpartum hemorrhage, Cesarean delivery), we could not rule out the possibility that it was associated with an increased risk of placental abruption because of sparse reporting, power limitations, and heterogeneity of populations in the studies reporting this outcome (RR, 1.17 [95% CI, 0.93 to 1.48]). Pooling only among trials enrolling higher-risk pregnant women (the target for aspirin intervention) somewhat attenuated the potential harm but reduced the precision, and results remained heterogeneous (RR, 1.12 [95% CI, 0.86 to 1.46]; I^2=50.1%; p=0.14). Although not statistically significant, based on these estimates, the number needed to treat to harm (NNH) one person was 417 in women at high preeclampsia risk, assuming a baseline risk of 2.0 percent of women having an abruption (which was consistent with the Maternal-Fetal Medicine Unit [MFMU] trial). If a baseline risk of 1.5 percent is assumed (consistent with CLASP), then the NNH increases to 556 in women at risk of preeclampsia. The NNH across all trials, including women at low or average risk, was 297 assuming 2 percent abruption incidence, or 392 with 1.5 percent abruption incidence.[72,76]

Two observational studies on aspirin use during pregnancy had null findings for the potentially harmful outcomes considered, miscarriage and cryptorchidism.[77,78]

Included trials presented considerable variation in the timing of aspirin administration, although all trials initiated treatment after the first trimester (i.e., none before 12 weeks' gestation). We found no consistent effect of the timing or dosage of aspirin use. There was less variation in the instructions regarding when to stop aspirin prophylaxis. Of the 21 RCTs included in this review, the MFMU trial was the only one to instruct study subjects to terminate aspirin use if preeclampsia developed. Five studies explicitly stated termination dates (i.e., 2 weeks or 10 days before the estimated date of delivery, 34 completed gestational weeks, or 38 gestational weeks). Two studies did not clearly specify a termination point in their articles. The remaining 13 studies specified continued aspirin use until delivery. Planned discontinuation of aspirin versus continuation to delivery did not appear to be related to outcomes.

The evidence from this review was also unable to provide clear guidance on the ideal high-risk candidate for prophylaxis and how she might be identified in clinical practice. Methods for determining elevated risk of preeclampsia varied considerably across trials, which resulted in a highly variable incidence of preeclampsia in the control groups of each study (from 8% to 30%). Our exploratory analyses, however, found no consistent relationship between the effect sizes for any outcomes and the baseline risk of preeclampsia, although there was a correlation between the sample size and incidence of preeclampsia (as represented by the control group preeclampsia incidence).

KQ 1. Is There Evidence That Aspirin Reduces Adverse Maternal or Perinatal Health Outcomes in Women at Increased Risk for Preeclampsia?

Summary of Results

We did not find direct evidence that low-dose aspirin use improved any maternal health outcomes related to preeclampsia in women at elevated risk, although power was limited for these relatively rare events (**Table 2**). We did find evidence of improved perinatal health, however, with 20 percent lower rates of IUGR (95% CI, 0.65 to 0.99; k=13; n=12,504; I^2=36.9%) and 14 percent lower rates of preterm birth (95% CI, 0.76 to 0.98; k=10; n=11,779; I^2=33.2%) in women randomized to low-dose aspirin, and no effect or a possible slight reduction in perinatal mortality (**Figures 3** and **4**, **Table 3**). The presence of small-study effects in the body of evidence for these outcomes, however, might mean that the magnitude of benefit for all fetal outcomes is lower than the findings from pooled analyses indicated.

Maternal Health Outcomes

Maternal health consequences of preeclampsia are extremely rare and include eclampsia, HELLP syndrome, organ failure, and death. Trial data did not allow us to test the effect of low-dose

aspirin prophylaxis on these serious direct maternal health outcomes (**Table 2**). Pooled analysis (k=10 studies;[58,59,61,64-70] n=10,419) indicated no difference in the Cesarean delivery rate for women taking aspirin compared with placebo (RR, 0.92 [95% CI, 0.79 to 1.08]; I^2=24.9%) (**Figure 7**).

Perinatal Health Outcomes

For perinatal mortality, the pooled estimate from 10 trials in high-risk women[57-62,65,68,70,71] (n=12,240) suggested a potentially reduced risk with low-dose aspirin use (RR, 0.81 [95% CI, 0.65 to 1.01]; I^2=0%) (**Figure 5**). Although pooled results do not firmly establish a mortality benefit, they significantly dampen concern about this potential serious harm from aspirin chemoprophylaxis. Six of the 10 included studies suggested less perinatal mortality in the aspirin group than in the placebo group (**Table 3**).[57-61,65] Three of the four trials that estimated a possible harm had sample sizes of 100 or less per arm.[62,68,70] While the fourth study that estimated a possible harm was somewhat larger (around 280 per arm), it also included the largest dose of aspirin (150 mg).[71] This study also enrolled women later in pregnancy (22 to 24 weeks' gestation) and was the only study using readings of uterine artery pulsatility to determine preeclampsia risk. We discuss harms in more detail under KQ 3.

Given the consistency of risk estimates between the two large trials and a pooled result with very low heterogeneity, a 20 percent reduction in perinatal mortality would not be ruled out. Additionally, we found no evidence of a small-study effect for this outcome (**Appendix F Figure 1**). Instead, we point out a Type II risk of incorrectly accepting a null finding for perinatal mortality. Our power for detecting a beneficial effect for perinatal mortality was likely insufficient because the event is rare; post hoc power calculations suggest that pooled analysis had only 50 percent power to detect a 20 percent difference in mortality. Additionally, when we conducted sensitivity analyses removing the women who were enrolled in the CLASP trial based on elevated risk of IUGR only, the effect estimate and CI were significant (RR, 0.79 [95% CI, 0.62 to 0.99]; k=10; n=11,136) (**Appendix F Figure 2**).

While the pooled result suggested a 20 percent benefit in reduced risk of IUGR (RR, 0.80 [95% CI, 0.65 to 0.99]; k=13 trials;[57-61,64-71] n=12,504), the estimates from the two large trials were not consistent (**Figure 4**).[57,58] Indeed, the large U.S. trial was the only included study that reported an IUGR estimate greater than 1 (RR, 1.19 [95% CI, 0.93 to 1.52]).[57] When we removed the large U.S. trial from our sensitivity analysis (since it was an outlier and the only one to stop aspirin upon the development of preeclampsia), the size of the effect remained similar (RR, 0.78 [95% CI, 0.64 to 0.93]) (**Appendix F Figure 2**). All other trials reporting IUGR had estimates indicating an aspirin benefit, but only one recent study conducted in Spain had significant results (RR, 0.49 [95% CI, 0.28 to 0.87]).[59] For IUGR, heterogeneity was low to moderate with the large U.S. trial (I^2=36.9%; p=0.09) and low without it (I^2=10.7%; p=0.34) (**Figure 4** and **Appendix F Figure 3**). We found evidence of a small-study effect based on the funnel plot and formal statistical test (Peter's p=0.14) (**Appendix F Figure 4**). Given the possibility of publication bias exaggerating the effect size and the inconsistency in the MFMU trial, it should be pointed out that further results could change this finding (to as much as a 51% reduction or a 31% increase in IUGR with aspirin use in high-risk women).

There was evidence of a 14 percent reduced risk of preterm birth (<37 weeks' gestation) (95% CI, 0.76 to 0.98; k=10; I^2=33.2%) in a meta-analysis of 10 trials (n= 11,779) (**Figure 3**).[57-62,64,66,68,70,71] All included trials reported effects in the direction of an aspirin benefit, although only two attained significance—the largest trial, CLASP (RR, 0.90 [95% CI, 0.82 to 0.99]),[58] and the recently published Ayala trial (RR, 0.35 [95% CI, 0.15 to 0.80]).[59] Heterogeneity was low to moderate (I^2=33.2%; p=0.14), and we identified evidence of small-study effects for the outcome from the funnel plot and formal statistical tests (Peter's p=0.05) (**Appendix F Figure 5**). Thus, the actual benefit could be attenuated somewhat with further research. In stratified analysis, there was evidence of a possible greater benefit with 75 mg of aspirin or more compared with less than 75 mg (p=0.04); however, the result is confounded by study size, as both of the large trials used 60 mg of aspirin (data not shown).

We found a difference in the mean birth weight of infants born to mothers taking low-dose aspirin compared with placebo, with those assigned to aspirin having an average birth weight 130 g greater than those assigned to placebo in pooled analysis (95% CI, 36.22 to 223.33) (**Table 3**, **Figure 8**). The CLASP trial, however, found an attenuated mean birth weight increase with aspirin (33 g [95% CI, 1.08 to 64.92]).[58] Birth weight data were not reported for the large U.S. trial.[57] There was moderate heterogeneity (I^2=60.0%; p=0.01) in the pooled analysis of birth weight, and all but one trial[67] (n=86, with a 23% incidence of preeclampsia in the placebo group) reported effects in the same direction (of benefit). We found evidence of small-study effects similar to those observed for other perinatal health outcomes. Given these limitations, we are not completely certain of the beneficial effect on mean birth weight with aspirin treatment suggested by the meta-analysis.

KQ 2. Is There Evidence That Aspirin Prevents Preeclampsia in Women at Increased Risk for Preeclampsia?

Summary of Results

Meta-analysis findings indicated that low-dose aspirin was effective for preventing preeclampsia in the included trials of women at elevated risk for preeclampsia (**Figure 2** and **Table 2**). We must consider evidence of small-study effects, however, when evaluating this body of evidence, as the magnitude of the preventive benefit likely is smaller than the pooled estimate would suggest. Likewise, the optimal aspirin dosage and timing are not readily discerned from this body of evidence. Moreover, the available evidence was unable to offer much guidance on the best approach for identifying women at elevated preeclampsia risk and those for whom prophylaxis was most beneficial. Evidence of small-study effects limited our ability to draw definitive conclusions in stratified analyses because two large studies were often in the same strata.

Preeclampsia Prevention

The pooled estimate (k=13; n=12,184) for preeclampsia incidence indicated a 24 percent reduction (RR, 0.76 [95% CI, 0.62 to 0.95]) with moderate heterogeneity across studies (I^2=40.5%; p=0.064) (**Figure 2**). A significant reduction in preeclampsia was not observed in the

two largest trials, although both estimated about a 10 percent reduction in preeclampsia.[57,58] We found evidence of small-sample bias, with larger studies reporting smaller effect sizes (**Appendix F Figure 6**). Formal tests for small-study effects were significant (Peter's p=0.03). A downward trend in the size of the effect of aspirin on preeclampsia prevention was apparent in forest plots sorted by sample size and, to a lesser extent, by year of publication.

We did not find evidence in stratified comparisons that the timing of aspirin administration (<16 weeks) or the dose used had different effects on preeclampsia prevention (**Appendix F Figures 7** and **8**). The estimated risk reduction was greater in studies using more than 75 mg of aspirin (RR, 0.58 [95% CI, 0.36 to 0.95]) than those using less than 75 mg (RR, 0.85 [95% CI, 0.68 to 1.05]), but the CIs overlapped and the test for effect-size differences was not significant. Analysis of the effect of dosage, however, could be confounded by small-study effects, since both of the large studies used doses of 60 mg.[57,58] The results of stratification are likely affected by the more modest effects seen in the two large studies relative to the remaining trials. Moreover, we did not find evidence of a dose-response relationship. Studies identifying women at elevated risk of preeclampsia using a clinical test, either alone or in addition to patient history, had a smaller pooled risk of preeclampsia than did studies relying solely on patient history (p=0.02) (data not shown). The six studies using clinical tests, however, were primarily small (n<150), except for one trial (n=554), and aspirin tended to be used later in pregnancy.

KQ 3. What Are the Harms of Aspirin Use During Pregnancy?

Summary of Results

We identified six RCTs that evaluated the harms of aspirin use to prevent preeclampsia in women at low or average preeclampsia risk[72-76,79] (n=10,855) that were not included for KQs 1 or 2. These six trials were considered in combination with 13 RCTs of 13,489 women at elevated risk that we included in our evaluation of KQs 1 and 2 (**Table 4**).[57-62,64-68,70,71] We also included two good-quality observational studies that met our inclusion criteria.[77,78] Based on data from these 19 RCTS and two observational trials, we found limited evidence of harms, particularly in women at high risk for preeclampsia, who would be the target population for aspirin chemoprophylaxis. While we could not rule out a risk of increased perinatal mortality with aspirin chemoprophylaxis due to power limitations, analyses limited to the intervention target population were reassuring, as the possible risk was attenuated and suggestive of potential benefit rather than harm. For abruption risk, there was no difference between groups in pooled analysis of all included studies of women at low, average, and high preeclampsia risk. Additionally, this effect size was attenuated when limited to women at elevated preeclampsia risk. Suggestion of a higher likelihood of harms when analyses are limited to low- or average-risk women suggests caution for aspirin chemoprophylaxis in such women. Comparison of other maternal and fetal bleeding outcomes between aspirin and placebo groups provided no evidence of harm from low-dose aspirin use beginning during the second trimester of pregnancy. Most studies instructed women to continue taking their allocated medication until delivery.

Perinatal Mortality

We conducted a meta-analysis of perinatal mortality including 14 of the 18 trials[57-62,65,68,70-75] of aspirin use in high- and average-risk women reporting perinatal mortality events (three additional high-risk trials[64,66,67] and one average-risk trial[76] reported on the outcome but had no events) (**Figure 5**). We identified no small-study effect on pooled estimates (**Appendix F Figure 1**). Pooled results suggested no effect on perinatal mortality (RR, 0.92 [95% CI, 0.76 to 1.11]; I^2=0%), although the possibility of increased perinatal mortality could not be completely ruled out because of power limitations (**Figure 5**). There was, however, evidence of a difference in estimated risk according to whether the baseline population was recruited as high preeclampsia risk or not as high risk. The effect-size difference test by recruitment risk status was statistically significant (p=0.01). In analyses stratified by preeclampsia risk, perinatal mortality tended toward a reduction with aspirin use in women at elevated preeclampsia risk (RR, 0.81 [95% CI, 0.65 to 1.01]), but an increased risk with aspirin use in average-risk populations (RR, 1.33 [95% CI, 0.90 to 1.96]) (**Appendix F Figure 9**). These results support no or very low perinatal mortality harm likely with low-dose aspirin prophylaxis when limited to women at increased preeclampsia risk, but we have less confidence that increased perinatal mortality with aspirin use by average-risk pregnant women can be ruled out based on the evidence reviewed, as the CI included the possibility of an 11 percent increase.

Placental Abruption

Eleven trials (n=23,332) reported placental abruption (six trials in women at increased preeclampsia risk[57,58,61,64,68,71] and five trials in those at average risk[72-76]), with three high-risk trials reporting no events (**Table 4**, **Figure 9**).[61,64,68] Overall pooled results were not significant for abruption risk from low-dose aspirin use during pregnancy (RR, 1.17 [95% CI, 0.93 to 1.48]), although the effect estimate was in the direction of harm. While studies were somewhat heterogeneous (I^2=36.4%; p=0.14), the majority of studies estimated an increased risk of placental abruption with aspirin use. In analyses stratified by preeclampsia risk, the pooled estimate from studies of women at elevated preeclampsia risk showed no increased risk of abruption (RR, 1.12 [95% CI, 0.86 to 1.46]), nor did the estimate attain significance for studies of women at average preeclampsia risk (RR, 1.38 [95% CI, 0.84 to 2.28]), and the estimates were not significantly different (**Appendix F Figure 10**). We found no difference in the risk of abruption by aspirin dosage in stratified analysis (**Appendix F Figure 11**). When sensitivity analyses excluding the MFMU trial were conducted, because the protocol instructed women who developed preeclampsia to stop taking their medication, the risk estimate for the remaining four trials remained nonsignificant (RR, 1.35 [95% CI, 0.88 to 2.06]), but the effect size increased and heterogeneity was lower (I^2=31.9%; p=0.20).

Only one trial (n=3,135), which assigned women to 60 mg aspirin, reported an extremely elevated risk of abruption (RR, 5.56 [95% CI, 1.23 to 25.02]).[72] The study was conducted at seven U.S. sites, primarily in healthy nulliparous minority women. A number of differences in the study, including an unusually low abruption rate, may have contributed to the risk estimate. The estimate had very low precision, and the CI included the pooled effect estimate.

Maternal Bleeding

Evidence from pooled analysis of nine trials (six elevated preeclampsia risk,[57-59,64,70,71] three low preeclampsia risk[72,74,75] [n=22,760]) indicated no increased risk of postpartum hemorrhage (RR, 1.02 [95% CI, 0.96 to 1.09]) (**Figure 10**). The result was the same regardless of the preeclampsia risk level, although all of the trials of women at elevated risk had an RR of less than 1 or very close to null.

We found no evidence that low-dose aspirin resulted in increased mean blood loss (n=2,748); all studies reporting the outcome found either slightly lower mean blood loss or equivalent amounts of blood loss between study groups. Only five trials[60,65,67,68,72] reported mean blood loss (four included SDs), however, and only one of these was rated good quality (**Table 4**).[72]

Fetal Intracranial Bleeding

We included 10 trials reporting on intracranial hemorrhage in neonates,[57,58,60,64-66,72,74,75,79] with four of these trials observing no events in either study group (n=22,457) (**Figure 6**, **Table 4**).[60,64-66] The outcome is rare, however, which limits our ability to detect treatment-group differences or observe events, particularly in smaller trials. No significant difference was reported in any trial, and all but one trial[57] observed more events in the placebo group. The pooled relative risk was 0.84 (95% CI, 0.61 to 1.16). The heterogeneity of the pooled analysis was low (I^2=27.1%; p=0.23), and there was not enough evidence to assess whether small-study effects were present, since only six studies reported events.[57,58,72,74,75,79]

In addition to reporting intracranial hemorrhage, some trials reported other types of bleeding events in neonates (i.e., cephalohematoma, any bleeding disorder). These results were rare, however, and the results were often inconsistent (**Table 4**). Two trials[66,72] reported the incidence of cephalohematoma but found conflicting results. One large trial of average-risk nulliparous women[72] (n=3,135) reported more events in neonates of mothers taking aspirin than neonates of mothers taking placebo (4.6% vs. 3.7%), while another trial of women at risk of developing preeclampsia[66] (n=65) reported the opposite finding of more events in babies of mothers taking placebo (0% vs. 3.1%). Two large trials conducted in average-risk women reported rates of any neonatal bleeding disorder, but these trials also found inconsistent results. One of these trials[72] (n=3,135) reported more events in neonates exposed to aspirin (7.0% vs. 6.5%), whereas the other trial[75] (n=3,647) reported slightly more events in neonates of mothers taking placebo (0.5% vs. 0.6%). Neither of these differences were significant. Rates of major hemorrhage in the neonate were reported in one trial of average-risk women (n=3,294), but this trial found no difference between treatment groups.[74]

Birth Defects and Developmental Outcomes

Only one study of possible birth defects from aspirin met our inclusion and quality criteria. This trial indicated that the rates of cryptorchidism were not different in male infants exposed and unexposed to aspirin in utero (**Table 5**).[77] Followup data sites in the United Kingdom and Canada from the largest RCT on low-dose aspirin in women at elevated preeclampsia risk

reported on developmental outcomes of the infants at age 12 months (n=4,168; U.K. followup data) and 18 months (n=4,365; U.K. and Ottawa followup data). This trial found no treatment-group differences in hospital visits, gross motor development, or height and weight measurements.

Other Reported Harms and Adverse Events

In addition to the main harms of aspirin evaluated across multiple studies, there were also reports on other harms. For the most part, these harms or the absence of harms provide assurance of the safety of aspirin during pregnancy. The large trial conducted in Barbados[75] reported no differences between rates of prenatal hospital admission, duration of hospital stay, induction of labor, or transfusion. In neonates, this trial reported no differences in admission to the special care nursery, duration of hospital stay, or bleeding problems. Similarly, in a large U.S. trial,[72] there were no significant differences in change in hematocrit or need for transfusions between the treatment and placebo groups. There were no cases of bleeding complications in women who received aspirin and epidural anesthesia. There were no differences in instances of cephalohematoma, cerebral hemorrhage, petechiae, purpura, excessive bleeding with circumcision, any bleeding disorders, or need for transfusion between the neonates in the two study groups. While less detail was provided, the same was reportedly true in the MFMU trial:[57] there were no differences in any adverse events in either mothers or neonates that were related to aspirin prophylaxis. The CLASP trial provided considerably more detail with regard to discussion of harms.[58] There was not a significant difference in rates of spontaneous labor, but women in the aspirin group were slightly less likely than the placebo group to require a Cesarean delivery during labor (p=0.08). In women who received epidural anesthesia, there was not a significant difference in instances of complications associated with the epidural between the study groups. In the aspirin-treated group, significantly more women received blood transfusions after delivery (4.0% vs. 3.2%). The increased use of transfusion was not associated with different rates or severity of postpartum hemorrhage. Finally, there were fewer cases of infants admitted to special care units in the treatment group (p=0.09), and the duration of stay was similar between treated and untreated infants.

Seven trials reported adverse events during the trial.[58,62,65-67,69,71] These data were insufficient, however, to fairly evaluate differences between treatment groups within or across trials. In their followup to Gallery's study, Leslie and colleagues reported two neonatal deaths, both in the placebo group, one from severe hyaline membrane disease and one from *Staphylococcus* epidermis septicemia.[80] One patient in Villa's trial experienced sudden deafness in one ear at 24 weeks' gestation. As a result, treatment was suspended and it was revealed that the patient was in the placebo group.[69] In the CLASP trial, one woman in the treatment group died 2 days postdelivery of a pulmonary embolus.[58] McParland and colleagues reported on one infant in the aspirin treatment group who died after a cord accident during labor.[65] Schiff reported one case of maternal endometritis in the treatment group that led to a sepsis workup of the neonate.[66] One neonate in the trial conducted by Vainio had hydrocephalus and meningomyelocele; this infant was enrolled in the treatment group.[67] In most cases these singular adverse events were found to be unrelated to treatment. (Aspirin treatment begun after the stage of embryogenesis would not be related to certain types of malformations.) Two studies reported women dropping out of treatment due to itching of the throat and epigastric pain.[67,71]

Reasons for Withdrawal

Trial participants withdrew from treatment for a variety of reasons. Participants frequently withdrew for nonmedical reasons, such as relocating, changing their minds about trial participation, or noncompliance with treatment. Medical reasons for withdrawal included conditions such as increased bleeding time, increased activity of aspartate amino transferase in serum, urticaria, or epigastric pain. Finally, women also withdrew from trials after miscarriage or the termination of pregnancy.

CHAPTER 4. DISCUSSION

Overall Summary

We found evidence that prophylaxis with low-dose aspirin beginning after the first trimester of pregnancy is beneficial for perinatal health outcomes in women at elevated risk of preeclampsia (**Table 6**). Specifically, we found a modestly reduced risk of preterm birth and IUGR in this group of women. While available evidence suggests that there is a reduced risk of perinatal mortality, the CI crossed null. The risk of incorrectly accepting a null result for perinatal mortality, however, is high because of low power to detect differences for this outcome. Consistent with lower risk of preterm birth (spontaneous or induced before 37 weeks) and IUGR, we also identified a significant difference in birth weight, but the evidence for this outcome is less convincing.

The observed pooled result for preeclampsia prevention supports the causal pathway for the direct health outcome benefits observed: the risk of preeclampsia was reduced by nearly one quarter with low-dose aspirin use initiated after the first trimester. Nonetheless, our confidence in the magnitude of the pooled result is tempered by the fact that estimates from the two largest trials were very modest and not statistically significant. Based on those trials, however, a 10 percent or greater reduction in preeclampsia would be a conservative interpretation of this body of evidence, given the consistency of the effect size in the large trials and the results of pooled analysis. This reduction in preeclampsia, which may manifest as delayed onset for some women, likely underlies the observed reduction in poor perinatal health outcomes.

There do not appear to be significant harms associated with low-dose aspirin use during pregnancy, although we cannot disregard the possibility of increased abruption risk. Based on the included trials, we also did not identify a risk from other bleeding-related complications, such as postpartum hemorrhage, maternal blood loss, and neonatal intracranial or intraventricular bleeding. Findings from observational studies on cryptorchidism and miscarriage risk were null. While the evidence on long-term outcomes for offspring from in utero aspirin exposure (low-dose) is limited, followup data from one large RCT was reassuring.

The NNTs for preeclampsia, IUGR, and preterm birth calculated from the midrange of study estimates of risk for each outcome are less than 50 (**Table 7**). The NNT decreases to less than 25 at the higher levels of risk occurring in some included studies. Even at the lowest levels of risk, the NNT was 42 for preeclampsia, 71 for IUGR, and 65 for preterm birth. On the other hand, the NNH for abruption would be much higher (and estimated from a nonsignificant pooled effect). Considering data from all trials and assuming a 2 percent abruption rate, 294 women would need to be treated for one case of abruption to occur. Based on the estimate for women at risk of preeclampsia, even more women would need to be treated to potentially incur one additional case of abruption (NNH=417). The NNH values are helpful to bound potential harms, even in the absence of a statistically significant result for abruption.

Other Systematic Reviews

The findings of our review are consistent with the results of the most recent Cochrane review,[47] which included 65 trials (1965–2007). Our findings are also consistent with those from an individual meta-analysis[49] that analyzed data from 31 RCTs (32,217 women; 32,819 infants). Both reviews were limited to trials of women at elevated risk for preeclampsia and included studies that combined aspirin with other antiplatelet medications. Neither review was limited to placebo-controlled trials. The Cochrane review reported on risk of bias but did not exclude studies for quality concerns. The individual meta-analysis, on the other hand, did exclude trials with high potential for bias. Our review found very similar effect estimates for preeclampsia, IUGR, preterm birth, and perinatal mortality, especially when compared with the individual meta-analysis. This result was apparent despite differences in study inclusion criteria and our extension of the search period. Only two new trials published since 2007 met our inclusion criteria.[59,69] A more recent review that included 32 trials conducted in women at both average and elevated risk for preeclampsia found a substantially reduced risk of preeclampsia (RR, 0.47 [95% CI, 0.35 to 0.65]) and IUGR (RR, 0.44 [95% CI, 0.30 to 0.65]) when initiating treatment before 16 weeks.[81] The nine studies included in the <16 weeks strata, however, all had fewer than 250 participants, and most had far fewer. As such, small-study effects may have influenced these findings. Similar to the other reviews, we found no difference in effects by aspirin dosage. Other published reviews of this topic have based their findings on smaller, select subsets of trials, and have provided limited explanation of reasons for exclusions.

There was a notable finding from the Askie (2007) individual patient meta-analysis that was not possible to assess in our meta-analysis because the variable was not available in the published literature.[49] The individual patient-level analysis found a 21 percent (p=0.01) reduction in the need for assisted ventilation of infants after delivery in women assigned to the aspirin treatment group.

Clinical Importance of Changes in Outcome Measures

While the estimated effect sizes were modest in pooled analyses, we found benefits for averting critical health outcomes. The possibility that a benefit for perinatal mortality is present could not be ruled out, and indeed the body of evidence weighs in favor of this being a true effect. While the significant benefits for preterm birth and IUGR would likely translate into reduced risk of perinatal mortality, the power to detect this rare outcome prevented us from detecting a statistically significant effect. In sensitivity analyses, however, we removed women entered into the CLASP trial based only on their risk for IUGR and not preeclampsia, and the benefit for perinatal mortality obtained statistical significance (**Appendix F Figure 2**). As discussed, there is considerable risk of incorrectly accepting a null finding for this outcome. Even if modestly effective, prophylaxis with low-dose aspirin in women at elevated risk of developing preeclampsia would likely prevent perinatal deaths, IUGR, and preterm birth.

There is considerable benefit to be gained from preventing IUGR and preterm birth because of short- and long-term health associated with these conditions. Preterm birth is the cause of 70 percent of neonatal mortality and 75 percent of neonatal morbidity in developed countries.[82]

Because the brain and lungs are the organs most affected by preterm birth, short- and long-term respiratory problems and neurological impairments are common in preterm infants.[82] Compared with infants born at term, preterm neonates have higher rates of intraventricular hemorrhage, respiratory distress, infection, seizures, and hospital readmissions.[82,83] With regard to IUGR, infants born at term (37 weeks) with low birth weight are more likely to have low Apgar scores, respiratory distress, seizures, and sepsis in the postnatal period and a greater risk of severe physical or neurological disability in adulthood.[82,83,84] IUGR and SGA also have been associated with decreased cognitive function; lower educational, occupational, and economic attainment; and increased mortality in young adulthood.[82,83,85]

While we did not find evidence of direct maternal health benefits, prevention of poor perinatal health outcomes could confer considerable benefits to maternal (and possibly paternal) quality of life. Further, preventing preeclampsia in women could have benefits due to reductions in the medicalization of the pregnancy and birth processes.[86] Medical interventions can affect mental or psychosocial health.[14,15] There is evidence that obstetric interventions and pregnancy complications are associated with increased risk of posttraumatic stress and poorer mental health after childbirth.[87-90] There is also evidence that preeclampsia is associated with poor psychosocial outcomes, posttraumatic stress syndrome, and postpartum depression,[89,91-93] with fetal or neonatal morbidity and mortality contributing to this relationship. A broader concept of maternal health might also consider the stress of caring for a preterm infant admitted to neonatal intensive care or a child with long-term health problems associated with early birth.

A number of studies have found associations between preeclampsia and long-term cardiovascular health outcomes in women and their offspring.[26,94] Current estimates suggest a possible doubling or tripling of cardiovascular disease risk in women who have had preeclampsia during any pregnancy.[95,96] These risks are considerably higher in women who had early-onset preeclampsia.[97] Long-term observational studies cannot ascertain whether differences in cardiovascular disease and mortality in women with a history of preeclampsia arise from underlying risk profiles that potentiate both, or whether preventing preeclampsia could reduce the risk of cardiovascular disease later in life. There is evidence that preeclampsia can cause transient and persistent endothelial injury, suggesting potential direct effects.[94] Two recent case-control studies, for example, found a higher rate of white-matter lesions in women with a history of preeclampsia compared with matched controls.[98,99] Subclinical damage to the brain and endothelial damage may occur from the cardiovascular strain and metabolic perturbations of preeclampsia. Whether these changes are responsible for increased long-term cardiovascular disease and mortality risk for the mother or affect the offspring of preeclamptic pregnancies is currently unknown. If this relationship were established, the lifetime benefit of aspirin prophylaxis to prevent preeclampsia or reduce its severity would be even greater than currently understood.

Perspectives on the Large Trial Evidence on Benefits

The studies included in our systematic review had considerable variation in the methods they used for identifying women at elevated risk of preeclampsia, the dose of aspirin used, the timing of treatment initiation, and the sample size and geographic location of the trials (**Appendix E**).

Two large trials provided the bulk of the data for pooled estimates of potential benefit.[57,58] Three additional large studies were added for evaluation of harms.[72,74,75] Smaller studies, many of which were rated as good quality, tended to have larger effect sizes. Therefore, we focus on consistency issues in the large trials, while acknowledging that the smaller trials also weigh into the pooled results and have important merits in terms of the ability to closely monitor and carry out study protocols. All of the large trials were national multisite studies[57,72] or international collaborations,[58,74] except one trial that we included only for harms.[75]

MFMU Trial

The MFMU trial is a large U.S. trial that had considerable influence on the pooled results.[57] The trial, however, has some unique characteristics relative to others included in our review. Briefly, the trial of 60 mg aspirin was conducted in women at elevated risk of preeclampsia (n=2,503). Eligible women were recruited at one of 13 study sites, were 13 to 26 weeks pregnant, and belonged to one of the following predefined preeclampsia risk categories: 1) pregestational diabetes mellitus (n=471), 2) chronic hypertension (n=744), 3) current multifetal gestation (n=688), and 4) preeclampsia in a prior pregnancy (n=606). Women with diabetes and hypertension were analyzed with the diabetes group, but women with multifetal pregnancies along with diabetes or hypertension were excluded. Unlike the other included trials, the MFMU protocol instructed women to stop taking their medication if they developed preeclampsia, which limits the ability to observe any benefits that might accompany aspirin use in women once the condition develops.

The risk criteria used and the population recruited resulted in high preeclampsia incidence during the trial; in the control group, one in five women were diagnosed (20%). The majority of women were racial and ethnic minorities; more than half were black, with smaller numbers of Hispanic and white participants. However, there was considerable variation in the racial/ethnic composition of the risk groups. For example, a majority of the participants with diabetes were white (53%), whereas 71 percent of the women with previous preeclampsia were black, 4 percent Hispanic, and 25 percent white. Among study participants with multifetal gestations, 50 percent were black, 18 percent Hispanic, and 32 percent white. Similarly, among those with chronic hypertension, 61 percent were black, 12 percent Hispanic, and 27 percent white. The average BMI reported at baseline indicates that many participants were overweight or obese, particularly in the chronic hypertension group (mean BMI, 33 kg/m^2 [SD, 9]). In addition, reported smoking rates during pregnancy were high in women with diabetes (22%) and chronic hypertension (17%).

Women with chronic hypertension were the largest of the four at-risk groups enrolled in the MFMU trial. These participants also had the highest control-group rate of preeclampsia (25%) and the highest average BMI (mean BMI, 33 kg/m^2 [SD, 9]) and age (mean age, 30 years [SD, 6]) compared with the other risk groups (i.e., diabetes, multifetal gestation, preeclampsia history). This was also the only at-risk group for which the overall rate of preeclampsia was higher in the treatment arm than in the placebo arm. Thus, while aspirin had no benefit on preeclampsia in this group, chronic hypertension clearly is a strong risk factor for preeclampsia. The diabetes and preeclampsia history at-risk groups had effect sizes consistent with the overall estimates of preeclampsia found in the CLASP study, while the estimate for multifetal gestations

tended toward greater benefit (RR, 0.7 [95% CI, 0.5 to 1.1]). Consideration of subgroup effects was present from the beginning with the MFMU trial; study authors specified the four risk groups a priori, selected a sample size to allow for detection of a 50 percent reduction in preeclampsia incidence within risk groups, and randomized study subjects by clinic center and risk group. However, power was too low to support formal statistical tests of interaction for subgroup effects, as observed effects were far lower than those used in the power calculation.

There are a number of possible explanations for the chronic hypertension group having an inconsistent effect estimate compared with the other groups. First, the CIs for all risk groups contained the estimate for the hypertension group. As a result, chance differences could be responsible for these estimates, as multiple comparisons were made. The risk groups were defined a priori, however. Second, owing to the high BMI in this group, 60 mg of aspirin could have been an ineffective dose that may not have exerted any effect on the biochemical pathways influencing preeclampsia. Third, women with chronic hypertension may have a different subtype of preeclampsia that is less receptive to aspirin prophylaxis or may have been more likely to have subclinical preeclampsia at study enrollment. Indeed, 119 women had hypertension and proteinurea at the study start, and although insignificant, the magnitude of the estimated effect showed the least likelihood of a benefit of all subgroups reported (RR, 1.4 [95% CI, 0.8 to 2.6]). As others have suggested, preeclampsia may be an umbrella diagnosis that includes a number of different conditions that have similar manifestations but occur through different pathophysiologic pathways.[100,101]

The results of a large trial (n=1,009) that we excluded from this review because of setting (Brazil) also supports this interpretation.[102] This RCT examined the effect of 60 mg aspirin compared with placebo in women at elevated preeclampsia risk. Chronic hypertension was one of this study's primary eligibility criteria (defined as "detected before or during pregnancy"), and nearly one half of study participants were enrolled for this reason. While the overall results of the trial were null for all outcomes, a pattern of lower effect estimates in women with chronic hypertension, similar to the MFMU results, was observed in the trial's detailed subgroup reporting. Although the authors prespecified subgroup analyses (and randomized the study accordingly), they did not report formal statistical tests of interaction for this subgroup, probably owing to insufficient power and null findings. Absolute and relative risk reductions were also not reported. While the high rates of preeclampsia in women with chronic hypertension make them an attractive subgroup for prophylaxis, data from trials with a high proportion of women enrolled with hypertension raise the possibility that aspirin prophylaxis may not be beneficial.

The MFMU findings for abruption, IUGR, and intracranial fetal bleeding had effect estimates directionally inconsistent with the body of evidence. It was the only trial of women at elevated preeclampsia risk to have an effect size less than 1 for abruption risk. This was also the only trial with an effect size greater than 1 for intracranial fetal bleeding, and it was one of only two studies that had an effect size greater than 1 for IUGR (the other trial[65] was small [n=100] and had an equal number of IUGR cases in each study arm). While none of the risk estimates were significant, these inconsistencies further distinguish this study from the rest of the body of evidence. With regard to abruption, the MFMU trial had the smallest effect estimate for preterm birth prevention (RR, 0.93 [95% CI, 0.85 to 1.02]), and thus there was very little difference in the time at risk for abruption between the two study groups. In all of the other studies, more

women in the aspirin arm experienced longer pregnancies, which extended the period during which abruption could occur.

CLASP Trial

The largest included study was a multinational trial of 60 mg aspirin managed by a U.K.-based collaborating center (n=9,364).[58] While the CLASP Collaboration included 16 diverse study sites (e.g., Malaysia, Spain, United Arab Emirates, Hong Kong, Canada, Germany, United States, Sweden), two thirds of the study participants were recruited in the United Kingdom and some sites contributed as few as seven participants (United States). CLASP was designed as a pragmatic trial, wherein women were enrolled to prevent or treat preeclampsia and IUGR based on personal and/or medical history. Prior preeclampsia or IUGR, chronic hypertension, renal disease, or other risk factors, such as age, family history, or multifetal pregnancy were identified risk factors for preeclampsia. The study authors indicated that the "fundamental criterion for entry was that the responsible clinician was uncertain whether or not to recommend aspirin in the individual pregnancy." Treatment could begin as early as 12 weeks' gestation, and participants were instructed to continue the medication until delivery. Nearly two thirds of study participants began treatment before 20 weeks' gestation.

CLASP participants were categorized according to whether they were enrolled in the study for prophylactic or therapeutic reasons. For the purpose of our review, we included only the prophylactic participants in our pooled analyses where possible (7,974 women; 8,257 infants). This was not possible for abruption, hemorrhage, or intraventricular hemorrhage, for which prevention and treatment groups were not reported separately. The overall incidence of preeclampsia in the control arm of the trial population was 8 percent, relatively low but above the usual rates observed in the general population of obstetric patients (2% to 5%).

The CLASP trial outcomes were analyzed by attributes of participants, including the reason for study entry (preeclampsia with or without IUGR vs. IUGR only), gestation at entry, and parity. Based on baseline characteristics and results for women entered for prophylaxis of IUGR only, we postulated that including this subgroup might dampen the overall trial findings. Forty percent of women enrolled for prevention of IUGR only reported cigarette smoking, which was a much higher rate than in the group enrolled for prevention of preeclampsia (17%). Thus, some proportion of the women enrolled for IUGR prevention alone were likely included due to a history of IUGR caused by smoking or because they currently smoked, which many clinicians would have understood to be a risk for developing IUGR or SGA.[103,104] Thus, some of these women would not be considered candidates for aspirin prophylaxis of preeclampsia or associated outcomes. The event rate for preeclampsia was very low and not affected by aspirin in the 1,094 women entered into the trial for prevention of IUGR only. For all other outcomes, however, the results were further toward null or harm in the IUGR only group compared with women entered to prevent preeclampsia. In effect, the IUGR only prophylaxis group dampened the estimation of aspirin benefit across outcomes. Indeed, the results for perinatal mortality preventive benefit in women at risk of preeclampsia became significant (RR, 0.79 [95% CI, 0.62 to 0.99]; I^2=0%) when we conducted sensitivity analyses removing the IUGR only prophylaxis participants from the meta-analysis. Pooled estimates for IUGR and preterm birth shifted further from null, and results for preeclampsia were unchanged. There were very few cases of preeclampsia in the

IUGR only group, perhaps because smoking is associated with reduced rates of preeclampsia.[105] Thus, the CLASP trial results could be interpreted as conservative for estimation of benefits, as could our main meta-analysis. We were unable to run the sensitivity analysis for any of the possible harms other than perinatal mortality because data were not reported by reason for study entry. Whether smoking and its effects on preeclampsia and IUGR might complicate the results of other included studies, whether reported or not, will be discussed in greater detail below.

The size of the CLASP trial permitted analyses that are not possible with smaller studies and suggest a trend in the benefit of aspirin for preeclampsia related to the timing of disease onset and its severity. Given that fewer women assigned to aspirin delivered preterm, there was a longer period in which women were at risk for developing preeclampsia. Thus, the CLASP authors posited that the magnitude of benefit for aspirin in preventing preeclampsia at earlier gestations may be underestimated by the overall pooled estimate. These authors found a trend toward increasing effect sizes for preeclampsia prevention and severity with lower gestational age at delivery (approximated by the need for antihypertension and/or anticonvulsion therapy). The result of this post hoc analysis suggests that women at risk for early preterm birth may obtain more benefit from aspirin, an observation worthy of further primary research.

Risk of Harms From Low-Dose Aspirin Use During Pregnancy

Our review's findings related to harms are consistent with those of other reviews and large trials. We are unable to rule out the possibility of an elevated risk of rare harms, in part because of the rarity of the events and low power. Nonetheless, our findings confirm the importance of identifying a population of women at elevated risk of preeclampsia, as the two outcomes (perinatal mortality and placental abruption) for which estimates of increased risk approached clinical (but not statistical) significance were limited to or more strongly suggested in healthy populations at low or average risk for preeclampsia. That is, the risk of abruption and perinatal mortality both showed more than a 30 percent increase in events with aspirin use in healthy populations. This estimate is based on a small absolute number of events and was not statistically significant. In contrast, risk was either reduced (perinatal mortality) or showed a much smaller increase (abruption) in the trials of women at high risk for preeclampsia, which was also not statistically different from the null. Other adverse perinatal outcomes were examined in the two included studies, which found no increased risk of cryptorchidism in male infants or developmental delays in infancy through age 18 months.[77,106]

Our findings for placental abruption are consistent with those of other studies, although our interpretation may be a bit more conservative because we retained the possibility of increased abruption risk. A number of large studies and an individual-level meta-analysis[49] have concluded that there is not an increased risk of abruption. Only one large trial in our review found a significantly increased risk of abruption.[72] Characteristics of the study population could factor into the result, including: using nulliparity as the only preeclampsia risk criterion recruiting primarily racial and ethnic minority women (half of the study participants were black and nearly one third were Hispanic women), and an unusually low rate of abruption in the control arm (0.1%). National and international population-based studies report an abruption incidence of 0.5

to 1.4 percent in pregnant women.[107-111] The rate of abruption generally is greater in black women than white women, and has been increasing in black women. A 2005 analysis of the National Hospital Discharge Survey data from 1979 through 2001 showed that the rates of abruption have increased in both white and black women.[111]

Abruption cases are also not always easy to diagnose. Likewise, given its rarity, small errors in reporting or detection could have a large influence on observed rates. A 2006 analysis of hospital discharge data from 1997 to 2001 in Finland (n=47,742) showed that, in confirmed cases of abruption, vaginal bleeding was present in 70 percent of cases; abdominal pain/uterine tenderness/uterine tetanic contractions/hypertonic uterus were present in 51 percent of cases; and bloody amniotic fluid was present in 50 percent of cases.[110] In addition, fetal heart rate abnormalities were present in 69 percent of cases.[110] The U.S. National Library of Medicine reports that diagnostic tests include ultrasound (either abdominal or vaginal), blood counts, and fetal monitoring.[112] Definitive diagnosis requires examination of the placenta after delivery,[107] and this was not uniformly reported in the body of evidence.

Given that preeclampsia may be associated with a risk of abruption in both white and black women,[111] one would expect that reduced rates of preeclampsia with aspirin would also reduce rates of abruption; however, this relationship is not apparent in our data. This finding could raise concerns about the biological plausibility of beneficial findings. Conversely, the data might be explained by an increased gestational age in women taking aspirin, an outcome that was not available from the studies. Since an extension of pregnancy is associated with reductions in preterm birth, however, this slightly longer period at risk could result in a slightly elevated observation of abruption cases in the aspirin arm of the RCTs. If this were the case, the risk of abruption could not be said to be caused by aspirin, but instead by the extension of the period at risk due to desired prolongation of gestation with aspirin. Given these complexities, we are not able to either rule out or confirm a risk of abruption with aspirin prophylaxis in women at increased risk of preeclampsia using available data. We can suggest, however, that the NNH from abruption based on worst-case assumptions is considerably higher than the worst-case assumptions for NNT for all outcomes measured.

There is another body of literature that examines whether aspirin and nonsteroidal anti-inflammatory drugs increase the risk of birth defects. These findings are somewhat mixed, with many studies finding no increased risk, and there are important limitations to the literature.[113,114] We excluded one large (n=20,461) case-control study[115] of birth defects in the United States from our review because it ascertained aspirin exposure from parents when children were an average of age 18 months. The study would likely overestimate true risk because parents of children with birth defects are more likely to remember using aspirin and other potentially teratogenic medicines than parents of children with no birth defects. These data are worth mentioning, however, because this was a large study conducted in the United States whose other methods were acceptable. The study authors examined a wide range of birth defects and reported the adjusted odds of 12 different birth defects associated with aspirin use compared with no aspirin use. Specific adjustment variables varied, but usually included site, maternal age, race/ethnicity, folic acid supplementation, smoking, and other variables specific to the outcome of interest. While most birth defects were not elevated with aspirin use, odds increased by a factor of about 2 for anencephaly/craniorachischisis, anophthalmia/microphthalmia, cleft palate,

amniotic bands/limb body wall, encephalocele, and bilateral cataracts. Despite the large sample, the number of events was generally small in the aspirin-exposed group (<8 except for cleft palate). As such, this study's power was limited and the results were statistically significant for only some of these outcomes. Thus, while the data are inconclusive and subject to ascertainment bias, they do suggest that if an association between aspirin and birth defects exists, it is likely small. Furthermore, aspirin prophylaxis for preeclampsia is initiated after the first trimester, when embryogenesis is complete. Therefore, some types of birth defects would not occur, whereas in observational studies unable to adjust for the timing or dose of aspirin exposure, they would be present.

Discussion of Important Study Variables

Three study features varied considerably in the body of evidence and are important to consider in turn, as they have implications for interpreting the body of evidence and for clinical practice.

Determination of Preeclampsia Risk

There is currently no consistent accepted method for identifying which pregnant women are at an elevated risk for preeclampsia. The included clinical trials employed a range of approaches for determining preeclampsia risk, and the degree to which the inclusion criteria resulted in a high-risk population can be assessed by comparing the preeclampsia incidence in the control group across studies. The incidence of preeclampsia observed across the included studies of women at elevated risk ranged from 8 to 30 percent. These differences are not trivial, as the benefits and harms of aspirin prophylaxis appear to vary with preeclampsia risk. These large differences in baseline risk in selected high-risk women, however, are made more complicated in their interpretation by a very lopsided distribution of sample sizes in this body of evidence into two large trials, a few medium trials, and many small trials. The largest trial exhibited the lowest preeclampsia incidence (7.5%) of participants diagnosed,[58] while the second largest trial had close to the highest preeclampsia incidence (20%).[57] At least four factors may account for this variability: 1) different methods for determining elevated preeclampsia risk; 2) different demographic characteristic risk profiles of population studied; 3) different cutpoints/definitions of preeclampsia; and 4) different exclusion criteria (i.e., variable inclusion or exclusion of women with chronic hypertension or multifetal pregnancies).

The importance of accurately identifying which women are most likely to benefit from aspirin prophylaxis is highlighted by the possibility of a perinatal mortality benefit in the pooled analysis of trials of women at elevated preeclampsia risk, and no benefit or possible harm in low- to average-risk women in the stratified pooled analysis. Stratified analyses by level of preeclampsia risk indicated that the estimated risk of perinatal mortality from low-dose aspirin is lower in the population of women selected because of risk factors for preeclampsia compared with women at average or low preeclampsia risk. However, the difficulty of identifying appropriate, high-risk women for prophylaxis is illustrated by two findings—the high variability of actual preeclampsia incidence in selected high-risk women in the studies and the similar preeclampsia incidence in the low-/average-risk group of studies with some of the studies aiming to enroll women at elevated risk.

Our review did not find evidence of a relationship between the incidence of preeclampsia in the control group and the effect of aspirin prophylaxis. We found the highest incidence of preeclampsia in studies employing a clinical test to select participants (alone or with other risk factor considerations), but the effect of aspirin was not found to be greater based on whether a clinical test versus pregnancy and medical history were used to select the trial population. Effect sizes were similar across a range of preeclampsia incidence levels in the larger studies. Of note, however, three small trials using clinical tests had very high preeclampsia incidence (22% to 30%) and observed some of the largest preventive benefits of aspirin reported in the review.[66,67,70] We observed a correlation between study size and preeclampsia incidence; given the small-study effects in the body of evidence, we are limited as to the conclusions that can be drawn until larger studies replicate the findings of these small trials.

For example, in the Yu trial,[71] a measure of the uterine artery mean pulsatility index using transvaginal ultrasound uterine artery Doppler readings at 22 to 24 weeks of pregnancy identified a population of women at elevated risk of preeclampsia (19% incidence in the control group). In fact, only the trials using a clinical test as part of their preeclampsia risk criteria obtained preeclampsia incidence greater than 14 percent, except for the MFMU trial,[57] which used medical history and obtained 20 percent incidence. Many of these trials, however, began later during pregnancy because the predictive tests were not as useful early in pregnancy. Preeclampsia incidence was considerably lower in all other trials using medical history risk factors; CLASP preeclampsia incidence was only 8 percent.[58] The CLASP trial gave very loose instructions for determining trial eligibility, and uncertainty as to whether or not a patient might benefit from aspirin prophylaxis was an encouraged reason for inclusion.

While researchers continue to search for a physiologic or biochemical marker that can be used early in pregnancy to predict the development of preeclampsia, a suitable marker with good test performance characteristics remains elusive.[31,116,117] Uterine artery Doppler wave patterns have been used to further identify women at risk of preeclampsia who will go on to develop preeclampsia, but the test performance characteristics have been disappointing, and do not meet international standards for reliability and accuracy.[28,118] There is arguably value in employing a screening test with high false-positive rates to identify a population that would potentially benefit from aspirin prophylaxis, as long as the population is at greater risk of preeclampsia than would be identified by pregnancy history alone.[28] Moreover, if patients identified using tests of uterine arterial pulsatility or notching are at risk of a subtype of preeclampsia that is more likely to respond to aspirin treatment than some of the history-based risk criteria (e.g., chronic hypertension, IUGR-only history), the markers may offer more benefit than the test performance characteristics suggest. Unfortunately, a review of systematic reviews of the evidence on the test performance of potential predictors of preeclampsia, including clinical examination (BMI and diastolic blood pressure), biochemical indicators, and ultrasound measures (i.e., uterine artery Doppler notching, pulsatility index, resistance index, and combinations), found low quality and high risk of bias in many of the studies.[28] The authors summarized the state of the literature by stating "most tests claiming to predict preeclampsia have poor accuracy," and highlighted the importance of finding tests that minimize false-negatives more than false-positives. There is also considerable excitement, although insufficient population-based evidence, regarding the use of a combination of Doppler ultrasound with biomarkers for better detection rates.[119-124]

Current understanding of the mechanisms of action for low-dose aspirin to prevent preeclampsia and some clinical trial evidence suggest that earlier commencement of therapy may be beneficial.[125,126] Some studies of low-dose aspirin rely on uterine artery Doppler ultrasound to identify candidates for intervention.[69] Problems with this test-treatment combination have been noted; namely, the value of the test cannot be inferred from these studies, even if there is a finding related to treatment.[127] Moreover, a recent meta-analysis assessing the use of utero-placental Doppler ultrasound for improving pregnancy outcomes found no measurable benefit.[128] This may be because there are not clear guidelines or preventive actions consistently applied following abnormal readings.

The MFMU trial's process for determining preeclampsia risk identified a high-incidence population using very clear and categorical medical history criteria.[57] Investigators used medical and pregnancy characteristics or history to select women with pregestational diabetes, chronic hypertension, multifetal gestation, or prior preeclampsia. These factors are more strongly associated with elevated preeclampsia risk than some of the risk factors considered in other studies (e.g., age, BMI).[32,59,64,69] In addition, the MFMU trial was predominantly conducted among racial/ethnic minorities, for whom there are documented disparities in preeclampsia rates in the United States. It remains unclear whether women with underlying chronic conditions, who indeed exhibit higher rates of preeclampsia, are uniformly likely to benefit from aspirin prophylaxis during pregnancy. The evidence we reviewed hinted at the possibility that risk of preeclampsia related to chronic hypertension is less responsive to aspirin prophylaxis, as discussed above. The manifestations and mechanisms of preeclampsia pathophysiology are understood to differ between women with prepregnancy cardiovascular conditions and those without such chronic conditions.[101] The achievement of a high-incidence study population did not consistently result in a greater benefit of prophylaxis, underscoring the need to identify which of the elevated risk categories or individual characteristics account for the modest benefit observed in the pooling of trials.

A history of preeclampsia increases risk in subsequent pregnancies, and the severity is often greater with recurrence.[129] It is difficult to ascertain, however, if basing prophylaxis solely on this criterion would identify a population at sufficiently elevated risk to obtain a population benefit. While many of the trials included in this review used prior preeclampsia as one of the inclusion criteria, the reasons for entry were various and results were rarely reported by entry risk criteria.

Multifetal gestation is associated with a twofold to threefold increased risk of preeclampsia.[130] One included study in our review enrolled only women with twin pregnancies, but the sample size was insufficient to draw conclusions.[61] The MFMU results for women enrolled with multifetal pregnancies, however, had a larger estimate of preeclampsia prevention than the other risk groups (RR, 0.7 [95% CI, 0.5 to 1.1])[57] (formal statistical tests of subgroup differences were not conducted, since all effect estimates for the outcome were nonsignificant). Further research on the benefits for this known risk group is needed.

The current evidence base has tended to underrepresent nulliparous women by using prior pregnancy experiences as key risk selection criteria. While nulliparity is itself a modest risk factor for preeclampsia, the current evidence does not offer guidance for prophylaxis in healthy

nulliparous women. Indeed, a recent systematic review of all studies evaluating interventions for preeclampsia prevention demonstrated the extent to which studies mix nulliparous and multiparous women without accounting for potential differences in baseline risk, causal mechanisms, and statistical power and NNTs according to the different disease prevalence.[131] There is evidence from two large studies of healthy nulliparous women that the criteria for aspirin prophylaxis resulted in little benefit and elevated the risk of harms, suggesting the need for identifying subgroups at further elevated preeclampsia risk among nulliparous women.[72,74] Recent efforts to develop multivariable risk prediction models for healthy nulliparous women hold promise but require further development and validation.[40,132,133]

Identification of a bilateral notch using uterine artery ultrasound has not been found to have good test performance characteristics in systematic reviews or recent studies,[133,134] but combining multiple moderate predictors of risk may sufficiently identify a risk group that would benefit from aspirin among healthy nulliparous women. We conducted stratified analyses comparing women identified to be at risk using patient history versus those identified at risk using clinical tests (alone or in addition to patient history). Prevention of preeclampsia may have been greater in studies where clinical tests were employed. The greater benefit for preeclampsia prevention, however, did not extend to risk differences in health outcomes, and small study effects limit the conclusions that can be drawn. Further, clinical tests tended to be used later in pregnancy, suggesting numerous sources of potential confounding that could account for the difference.

The large individual-level meta-analysis conducted by the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration was unable to identify any risk group that benefited more from aspirin prophylaxis than others for preventing preeclampsia.[47] The only risk factor attaining $p<0.01$ significance for interaction tests was prior hypertension disorder of pregnancy. Compared with women without this history, there was potentially a greater aspirin benefit for perinatal mortality. Overall, however, there is an absence of clear guidance on the subset of women at risk of preeclampsia most likely to obtain a preventive benefit for the range of outcomes considered. A threshold of expected preeclampsia incidence (e.g., 10% to 20%) for different risk factors and combinations of risk factors contributing to preeclampsia incidence may be worthwhile to consider for decisions regarding prophylaxis.

Effects of Aspirin Dosage

The aspirin dosage used in the included trials ranged from 60 to 150 mg daily. Evaluation of differences in effect by the dose of aspirin using a 75 mg cutpoint revealed only one outcome with a significant difference; the preterm birth estimate of benefit was greater in studies using a dose of at least 75 mg. The results of all stratified analyses for dosage, however, were confounded by study size, as both of the large studies used only 60 mg of aspirin. Sorting forest plots of each outcome by aspirin dosage also did not present a pattern suggestive of a dose-response effect. The absence of convincing evidence for an effect of dosage is consistent with an individual meta-analysis based on studies of women at low and elevated preeclampsia risk that included all of the large studies we included in our review.[49] More recent systematic reviews confirmed the same result.[81,135] The recent Cochrane review, however, found greater benefit in studies using more than 75 mg aspirin doses compared with those using less.[47] Unlike the Cochrane systematic review, our trial did not include trials with other antiplatelet medications,

and we excluded studies of poor quality due to high risk of bias and those conducted outside of "High Development Index" countries that were included in the Cochrane review.

Timing of Aspirin Treatment

Evidence from our meta-analysis did not find that initiating aspirin treatment before 16 weeks conferred more of a benefit than starting later. Consistent with our results, an individual-level meta-analysis tested whether there was a benefit to beginning aspirin treatment before 20 weeks' gestation versus 20 weeks or later and found no difference.[49] In contrast, a review by Bujold[81] found a significant difference related to treatment timing, with women starting treatment before 16 weeks having reduced preeclampsia risk but not those starting at 16 weeks' gestation or later. Unlike our review, the Bujold review included studies of women at low and elevated preeclampsia risk (32 trials) and was not limited to placebo-controlled trials. There is some evidence that preeclampsia may result from problems with the process of trophoblastic invasion completed around 16 weeks of gestation.[3] Thus, initiating treatment before or during this process has been recommended due to the plausible mechanism of action.

We included two trials[59,64] conducted by the same research group that randomized women to 100 mg aspirin or placebo and to taking the medication at different times of day: upon awakening, 8 hours after awakening, and at bedtime. These trials' results strongly support a difference in effect depending on the timing of administration relative to the sleep-wake cycle. No preventive benefit was observed for women who took the aspirin upon awakening, but starting times that were later during the day did confer a substantial benefit. The studies included 24-hour blood pressure monitoring and found differential effects on the moderation of blood pressure based on the time of day aspirin was taken.

Other Factors Related to Aspirin Effectiveness

The effectiveness of prophylaxis may depend on how well the recommended dosage achieves its physiologic potential for a given woman's metabolism, physiology, and health behaviors. Variation in the average BMI of trial participants could complicate the evidence if the aspirin dose needs to be calibrated to individual physiological characteristics in order to be effective. One study used a protocol calibrating the dose to body weight (0.5 mg/kg), but this would have resulted in one of the lowest doses across all studies given the average weights reported.[67] Nonetheless, application of this concept may need to be more nuanced. Beyond differences in volume distribution of aspirin by BMI, the antiplatelet activity of low-dose aspirin is not as effective in obese women due to increased platelet reactivity compared with nonobese women.[136] Also, there is evidence that increasing the dosage of aspirin may not overcome higher platelet activity.[136]

Limitations in the Body of Evidence

Power

The most commonly reported harms and some of the benefits we evaluated were very rare events, which poses power constraints that limit our ability to draw conclusions (even after pooling) without an increased chance of incorrectly accepting a null hypothesis.

Small-Study Effects

Although there was no evidence of small-study effects for a few outcomes, such as perinatal mortality, the body of evidence demonstrates a likely influence of publication bias, an observation that has been suggested and supported by others.[47,49,57] Many small studies did not contribute to the pooled analysis due to no events for rare outcomes, such as perinatal mortality. This may contribute to the inconsistent results of the statistical tests for small-study effects on these outcomes.

Interactions With Cigarette Smoking

Considerable accumulated evidence indicates that smoking reduces the risk of preeclampsia.[105, 137] A 2012 study of data from the National Swedish Birth Register concluded that the risk of preeclampsia was reduced in women who smoked during pregnancy, and supported the causal interpretation of the observed inverse association between smoking during pregnancy and risk of preeclampsia.[138] Similarly, a 2009 study of more than 600,000 singleton pregnancies in New York City found that smoking was associated with a reduced risk of preeclampsia. No association was found for preeclampsia superimposed on chronic hypertension, however, which suggests that smoking is protective against preeclampsia only in the absence of chronic hypertension. Additionally, smokers who develop preeclampsia-related disorders have no increased risk of adverse birth outcomes compared with nonsmokers who develop the same conditions.

The current understanding of the mechanism of action is an effect of smoking on reducing the circulating levels of antiangiogenic proteins (such as sFlt-1) that studies have shown occur with exposure to the carbon monoxide in inhaled tobacco products.[137-144] A rise in these proteins is associated with the development of preeclampsia.[143] There is also evidence of a negative interaction between smoking and preeclampsia with respect to preterm delivery and birth weight. Smokers who develop preeclampsia have a lower risk of preterm delivery and a lower adjusted mean difference in birth weight than expected based on the independent effects of smoking and preeclampsia.[145] Thus, the relationship of smoking to preeclampsia and IUGR is complicated; smoking can cause IUGR and prevent preeclampsia, yet it may improve or at the very least make no difference for IUGR in women who have preeclampsia.

Advising women to stop smoking during pregnancy is standard practice and benefits maternal and child health.[146] The evidence related to smoking and preeclampsia, however, raises some important research considerations for preeclampsia prevention with aspirin and the related research. We do not currently know if the effectiveness of aspirin prophylaxis is affected by smoking and whether the effect of aspirin is more modest or less modest than the effect of smoking (as no clinical trial of smoking will ever take place). The first question could be investigated, and these results would have implications for counseling patients on the importance

of quitting smoking if recommending aspirin prophylaxis. If aspirin does not provide a net benefit in patients who smoke and do not quit during pregnancy, the risk of harms with aspirin should not be incurred. Thus, research is needed to better understand the common pathways and possible interactions or interference of smoking and aspirin prophylaxis. With regard to the research on aspirin and preeclampsia prevention, exposure to firsthand and secondhand smoke may need to be more carefully documented and analyzed as a potential effect-modifying variable.

Limitations in Our Approach

Excluding studies determined to be at greater risk of bias (low quality) could have caused us to inadvertently exclude some valuable information. By limiting our analysis to fair- and good-quality studies, however, we are better able to distinguish true effects from random variation and are also less likely to draw erroneous conclusions based on study bias.

We included only one good-quality study evaluating longer-term effects (i.e., cognition, growth) of in utero low-dose aspirin exposure on the outcomes of offspring. There are additional observational studies in the literature that offer hypothesis generating evidence regarding aspirin exposure during pregnancy and long-term effects. These studies, however, have limited applicability and quality issues. These studies were not included in our review because they contain fatal flaws, such as ascertainment of exposure after the outcome is diagnosed or observed. Many studies reporting on associations between aspirin exposure and fetal and longer-term outcomes also do not contain information on the dosage, timing, or regularity of exposure. Therefore, the substantial RCT data on women taking low-dose aspirin during pregnancy are more applicable for ascertainment of harms than observational cohort data. The drawback of this evidence, however, is that it does not offer much information on potential long-term harms that would not be apparent at the time of delivery. Only the CLASP trial reported long-term followup data, and it did not report these data for the entire trial sample. Another RCT of 50 mg of aspirin, which was not included in our review due to differential followup between treatment arms and suspected potential for ascertainment bias, conducted 18-month followup and found no harms with regard to development, disease, or malformations.[147]

Variation in Definitions of Outcomes

We pooled some outcomes that were defined differently across studies, with different thresholds for diagnosis. For example, IUGR and preeclampsia are not uniformly defined, as definitions are not standardized and have shifted over time. Attempts to diagnose IUGR rely on assessing whether an infant has realized its genetic growth potential. Assessment that an infant is SGA generally relies on assessment of normative weights for gestational age, with effort to adjust for race and sex. SGA neonates with birth weight below the 10th percentile or some other cutpoint are often judged to have IUGR.[148] The American College of Obstetricians and Gynecologists considers healthy fetuses who are at the lower end of the growth spectrum as well as those who have not reached their genetic growth potential due to pathological or genetic issues to have IUGR if their birth weight is below the 10th percentile.[149]

Notably, in the studies we reviewed, the definition of IUGR ranged from below the 3rd percentile to below the 10th percentile of birth weight for gestational age, with the latter definition being the most commonly used. The CLASP trial used the definition of below the 3rd percentile for IUGR,[58] and the large U.S. trial used the definition of below the 10th percentile.[57] The Royal College of Obstetricians and Gynecologists does not differentiate between IUGR and SGA. The American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynecologists consider the abnormal condition to be estimated or actual weight below 10 percent. Some studies used 2 SDs below the mean weight for gestation as the lower cutoff. This practice appears to be more common in European countries. Some studies did not clearly define the criteria used.

While preterm birth was defined as less than 37 weeks in most of the pooled studies included in our analysis, some studies also considered the effect of aspirin on births before 34 weeks. The Askie meta-analysis also used this cutpoint, but estimated a risk very similar to our finding, with a 10 percent risk reduction and similar NNT.[49] Similarly, preeclampsia is not always defined with the same cutpoints, especially for proteinuria.[3] Two types of urine sampling were used for diagnosis of proteinuria in the included studies: a 24-hour urine sample test and a urine dipstick test. The 24-hour urine sample is accumulated, while the dipstick test uses two or more point-in-time measurements of urine protein. The dipstick lacks the specificity and sensitivity of the 24-hour urine sample.[150] Among the studies included in our meta-analysis of proteinuric preeclampsia that described the diagnostic criteria, most used a cutpoint of 300 mg/24 hour or greater.[57,59,61,67,68,71] Schiff and colleagues used a urine sample cutpoint of greater than 500 mg/24 hour.[66] Several studies used dipstick tests with or without 24-hour urine sample testing; three studies defined preeclampsia with a dipstick test +2 reading,[57,71] and two studies used +1 as the cutpoint.[58,67] Other test cutpoints included a +3 dipstick and greater than 0.5 g/L proteinuria in the absence of urinary tract infection.[69,70]

The individual meta-analysis by Askie et al (2007) recoded the data from 26 trials to the same prespecified definition of preeclampsia, but found no difference in the results when analyses were conducted using the authors' own definitions.[49]

Analytic Limitations

Preeclampsia is known to pose a risk of abruption.[107] For severe preeclampsia, the risk has been found to be greater for black women than white women.[111] The observed rates of abruption in the included aspirin trials are consistent with population-level rates and lower than some estimates for black women.[111] Since none of the studies reported time-to-event analyses, the potential risk of abruption with aspirin could be influenced by a longer period at risk if pregnancy was extended, as suggested by the preterm birth and birth weight benefits of aspirin. We were unable to adjust for this possibility in the pooled analyses. Overall, time-to-event analyses may be preferable for this topic given that some outcomes (e.g., preterm birth) change the period the participant is at risk for other outcomes. Indeed, the CLASP findings related to a trend in effect sizes relative to the timing of preterm birth highlight the need to conduct more nuanced accounting for gestational time.[58]

Applicability of the Evidence to Clinical Practice

Few studies in the review were conducted in the United States, but limiting our search to trials conducted in "High Development Index" countries should minimize dissimilarities in prenatal and obstetric care that would render the results of this analysis of limited applicability. If there is a prophylactic effect of aspirin on preeclampsia, a difference in health outcomes should be observed regardless of the setting, as long as the RCT is of good or fair quality. Differences in case management may increase or reduce the likelihood of observing a negative health outcome with preeclampsia, but this would not vary by study arm, only the total events.

The degree of compliance with the study treatment was variable across studies, and might also differ for women who would not choose to enroll in an RCT. If women recommended aspirin prophylaxis outside the context of an RCT are less likely to consistently follow the daily regimen, the modest effects we observed could be dampened. Alternatively, and perhaps more likely, women recommended aspirin prophylaxis outside of the RCT context who are told it has been found effective for preventing poor perinatal outcomes may have higher compliance than observed in an RCT. Of the 23 studies included in this systematic review, almost half (n=11) reported some information on study regimen compliance. Of these 11 studies, eight reported compliance measures, typically defined as a proportion of tablets taken, but measures varied across studies. The percentage of study participants who took at least 80 percent of their pills was reported in the MFMU (79%) and Sibai (70%) trials.[57,72] The Yu trial reported the median percentage of tablets taken, which was 95 percent for both the intervention and control groups.[71] The CLASP trial found that 88 percent of participants continued study treatment for at least 80 percent of the time between randomization and delivery.[58] Overall, compliance rates were high.

In the absence of standard validated tools to identify women at increased risk of preeclampsia, there is a need for clinical guidance. We conducted a limited qualitative review of the evidence on preeclampsia risk factors, drawing upon overview articles,[2,32,129] as well as the 2011 NICE and WHO guidelines for preeclampsia prevention, to describe an approach for risk stratifying prenatal care patients. Until a validated screening algorithm is available, factors that can be ascertained in a prenatal visit early in pregnancy are most useful for guiding aspirin prophylaxis decisions; we therefore focus on medical history indicators of risk.

Medical and personal history risk factors that were used in many of the clinical trials contributing to our evidence review, as well as those well-established in the published literature since those trials were conducted, are provided to help clinicians identify women most likely to obtain aspirin prophylaxis health benefits (**Table 8**). The consistency and strength of evidence varies for risk factors. Those included are aimed at identifying a patient population with absolute risk of preeclampsia of at least 8 percent, consistent with the lowest preeclampsia incidence observed in the control group for the studies in our review of aspirin benefits. It is expected that further updates to the approach for determining risk will be necessary. In the future, a validated screening algorithm for preeclampsia prediction in both nulliparous and multiparous women may become available. Additional moderate preeclampsia risk factors that have been identified in the literature include sleep-disordered breathing in pregnancy (i.e., apnea, snoring), history of migraine headache, low exposure to paternal sperm (e.g., fertility treatments), systolic blood pressure greater than 120 mm HG at 15 weeks' gestation (in nulliparous women), and substantial

weight gain between pregnancies (i.e., BMI increase of 2+ points). Since this is an active area of research, the list included in **Table 8** is likely to be modified.

As noted by Simon et al (2013), most of the trials on the effectiveness of aspirin treatment combine nulliparous and multiparous women.[131] The effects of aspirin are broadly indicated to apply to women considered at increased risk for preeclampsia. The ability to identify which nulliparous women are at high risk for preeclampsia is limited. The strongest predictor of preeclampsia is prior preeclampsia, which cannot apply to women in their first pregnancy. Recent efforts to develop a model based on clinical risk factors for identifying elevated preeclampsia risk in nulliparous women could eventually provide guidance.[40] Once validated, this algorithm may assist in the identification of nulliparous women who may be candidates for aspirin prophylaxis.

Future Research Needs

We identified three ongoing trials comparing aspirin use with placebo in the prevention of preeclampsia (**Appendix B**). These trials are scheduled to be completed in the coming years (2014 to 2015). One of these trials, a large French trial with an estimated enrollment of almost 5,000 subjects, will test the efficacy of low-dose aspirin (160 mg/day) in nulliparous pregnant women selected as high risk by the presence of a bilateral uterine artery notch before 16 weeks' gestation. Another study, a U.S. trial with an expected enrollment of 220 women, will estimate the efficacy of low-dose aspirin (81 mg/day) in pregnant women identified as high risk by a first trimester multiparameter predictive model. The third study, conducted in Spain with a targeted enrollment of 270 women, will evaluate whether low-dose aspirin (150 mg/day) improves trophoblastic development, assessed during the third trimester in women defined as high risk by abnormal uterine artery Doppler. Preeclampsia is a secondary outcome measure in this third trial.

We identified four other ongoing trials related to aspirin and preeclampsia. These studies would not be considered using our review criteria, either because they include intervention arms that combine aspirin with other potentially active therapies or because they include comparison arms that use active substances. Two of the four trials are using combination therapies that include aspirin and low-molecular-weight heparin, one trial is comparing different doses of aspirin in women with a previous history of preeclampsia, and one trial is comparing aspirin with a dietary supplement (folic acid).

The results of these ongoing studies will contribute to the body of evidence to improve our understanding of the effect of aspirin use on preeclampsia. As the trials refine unique clinical screening tools to identify women at elevated risk and use higher dosages of aspirin, they will contribute to the evidence base, as will studies investigating the mechanism of action. These studies all initiate aspirin use early during the second trimester and may consolidate the evidence on the optimal timing. Given that different dosages and risk selection approaches are used across studies, however, disentangling the source of benefits and/or harms will remain a challenge. In addition, apart from the French trial enrolling 5,000 women, the small trials will likely contend with power limitations unless their enrollment criteria successfully identify a subset of women for whom a greater benefit can be obtained than that observed in our meta-analysis. The French

study will make a particularly important contribution if it is able to identify a subset of nulliparous women who are likely to experience preeclampsia and could benefit from prophylaxis.

The U.S. trial follows a trend in the literature on preeclampsia toward combining clinical testing with historical or pregnancy-related risk factors to determine women at high risk for preeclampsia. Current research seeks to validate a multiple variable model that has rigorous predictive value for preeclampsia. While none of these models has yet obtained the test performance validity level desired, they may identify women at sufficiently elevated risk for aspirin prophylaxis to be beneficial. There is considerable optimism, although insufficient population-based evidence, regarding the use of a combination of predictors, including maternal serum markers, pregnancy and medical risk factors, and ultrasound evaluation that would result in better test performance.[119-124] The need for rigorous evaluation of the effectiveness of test treatment combinations has also been clearly argued.[127]

Research might also pursue ways of individualizing the aspirin dosage and timing of administration most likely to exert a benefit for patients. Research using direct measures of the activity of aspirin and examining whether taking aspirin before bedtime increases its preventive potential hint at interesting possibilities for future RCTs. The large ongoing French trial will be the first of its size to use a protocol instructing women to take their study medication before bed.

The manifestations and mechanisms of preeclampsia pathophysiology in women without chronic conditions and those with prepregnancy cardiovascular conditions are understood to differ.[101] More primary research is needed to illuminate how preeclampsia arising from different risk factors develops and responds to aspirin intervention. The mixing of preeclampsia risk groups in RCTs is common and pragmatic. This approach, however, could mask important findings that would emerge with more homogenous and specific risk groups, unless a priori risk-based subgroups are built into sample size calculations and other aspects of study design. In addition, other interventions, such as diet and exercise modifications, could be more effective and present lower risk of harms for women at risk for preeclampsia because of high BMI.[30]

Finally, risk factors that are well-established in the literature were used as enrollment criteria for the RCTs we included. New literature exploring other medical history risk factors point to other possible risk factors that could be considered in future studies. For example, there is evidence of greater preeclampsia risk in women diagnosed with migraine headaches[35,151] and with asthma;[152,153] the risk may be particularly high for women with both conditions.[154]

Conclusion

While our systematic review of the evidence identified a likely benefit of low-dose aspirin for the prevention of preeclampsia and perinatal morbidity, many questions important for informing clinical practice guidelines remain. Additional research is important to answer remaining uncertainties, particularly since few trials have been conducted in the United States or in black women, who suffer the highest burden from the disease. While available evidence hints at prevention of neonatal mortality and the significant morbidity associated with preterm birth and

IUGR, harms associated with low-dose aspirin in pregnancy, particularly risk of abruption, are also a potential. Considerable evidence indicates that the rate and likelihood of those harms is considerably lower than the prophylactic benefits, particularly when women at higher risk for preeclampsia are successfully identified.

Our review suggests that the modest effect sizes seen in the two large trials are supported by the weight of the evidence, and we suggest that the CLASP and MFMU trials may even be at risk of underestimating the benefit due to the confounding influences of smoking, body weight, and aspirin dosage. While small-study effects were evident, the trials included in our review exhibit a fairly consistent pattern of effects indicative of some degree of benefit. It may be weaker in magnitude than the aggregate including small studies, but perhaps greater than the results of the CLASP and MFMU trials would suggest. The acknowledged challenge in applying the evidence on aspirin prophylaxis for preeclampsia to clinical practice remains predicting who is at risk and most likely to see a benefit from treatment.

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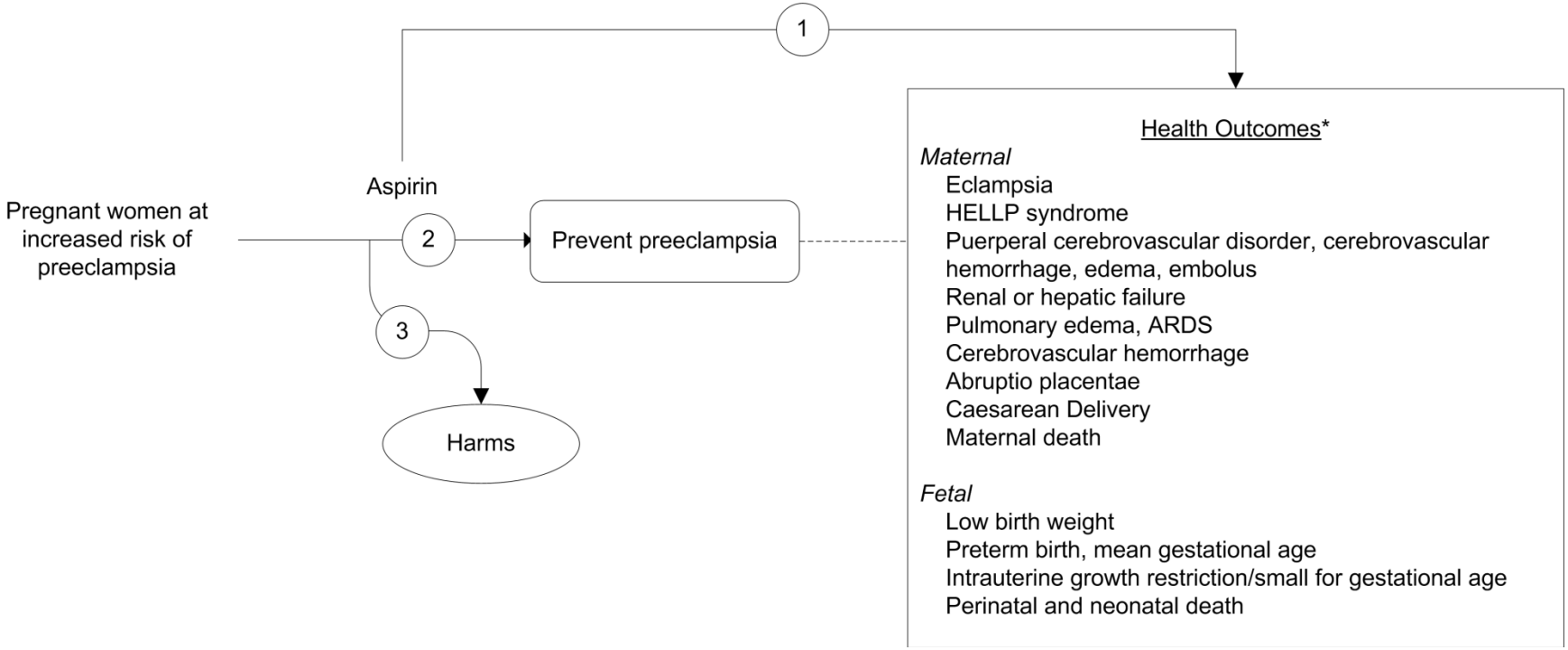
Figure 1. Analytic Framework



*Abbreviated list of health outcomes. For full list of outcomes please see Appendix A Table 1.

Figure 2. Pooled Analysis of Preeclampsia Sorted by Sample Size (Trials of Women at Risk of Preeclampsia)

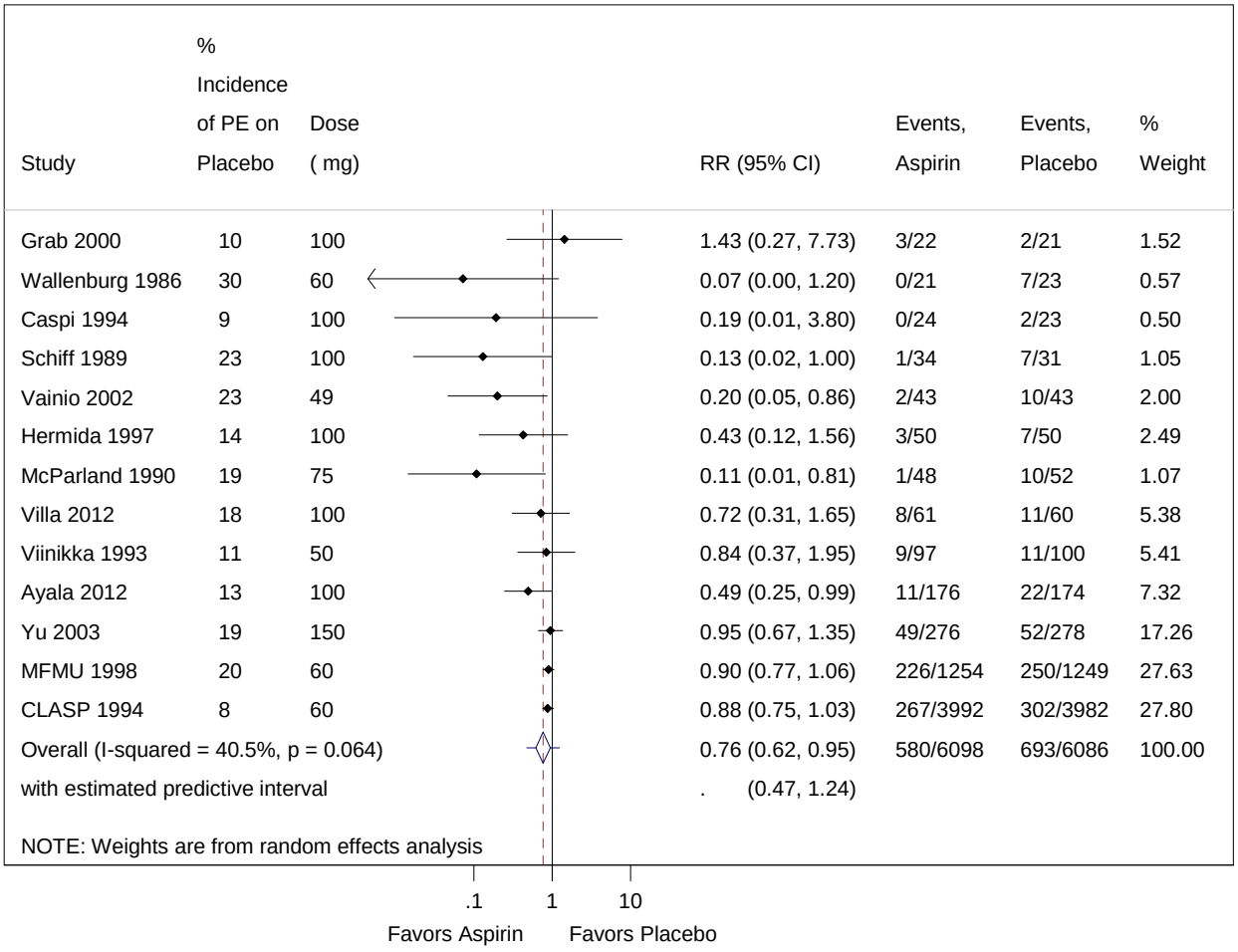


Figure 3. Pooled Analysis of Preterm Birth Sorted by Sample Size (Trials of Women at Risk of Preeclampsia)

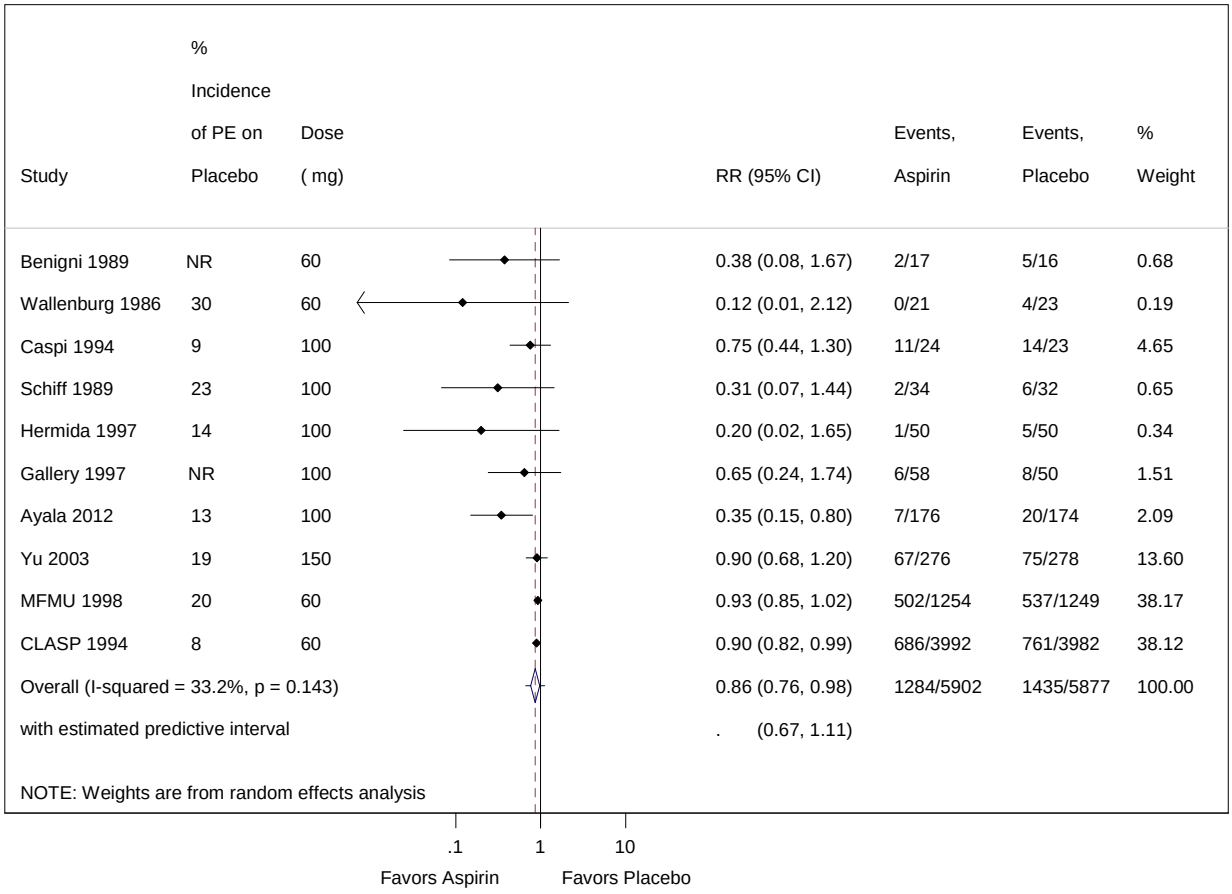


Figure 4. Pooled Analysis of IUGR Sorted by Sample Size (Trials of Women at Risk of Preeclampsia)

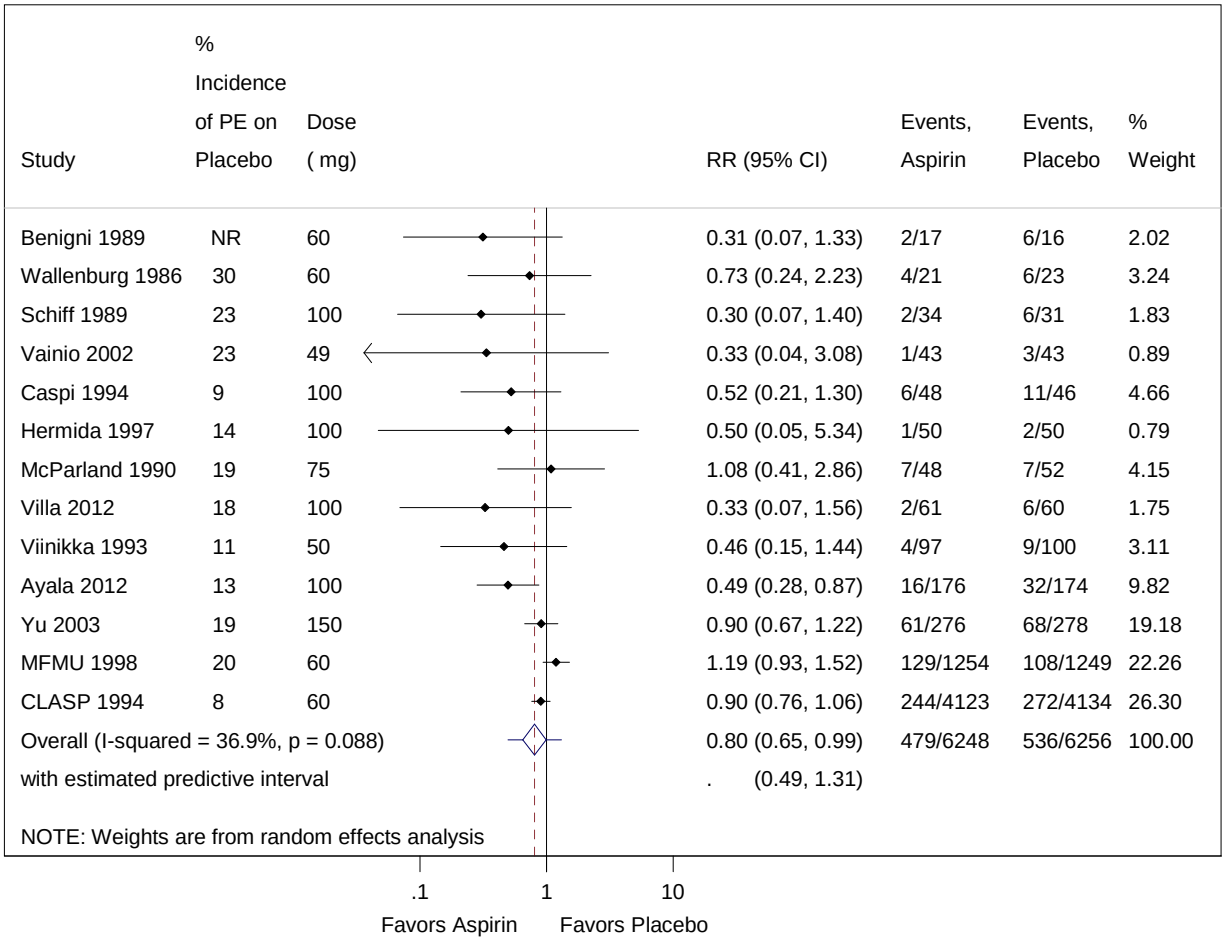


Figure 5. Pooled Analysis of Perinatal Mortality Sorted by Sample Size (All Trials)

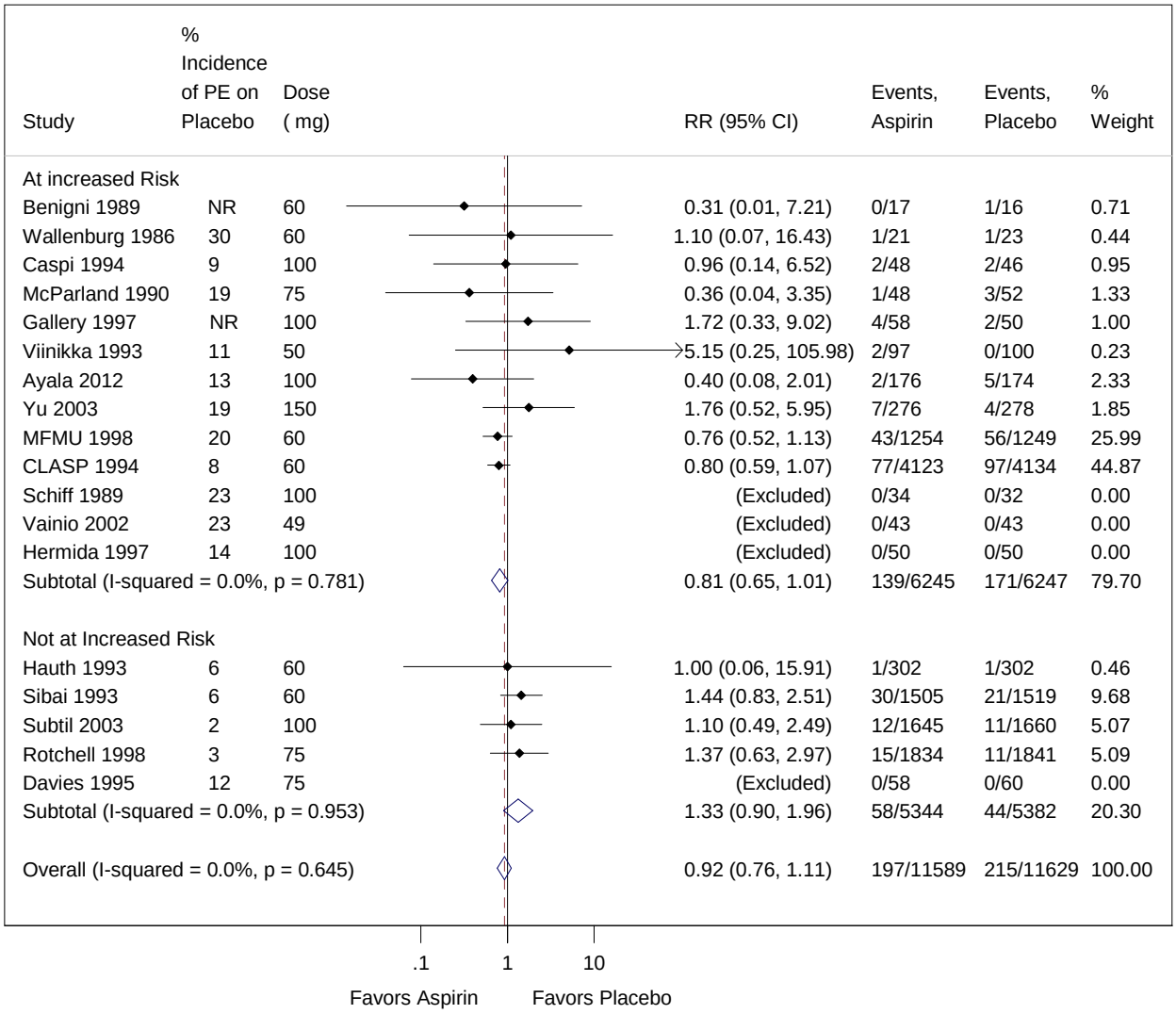


Figure 6. Pooled Analysis of Intracranial Fetal Bleeding Sorted by Sample Size (All Trials)

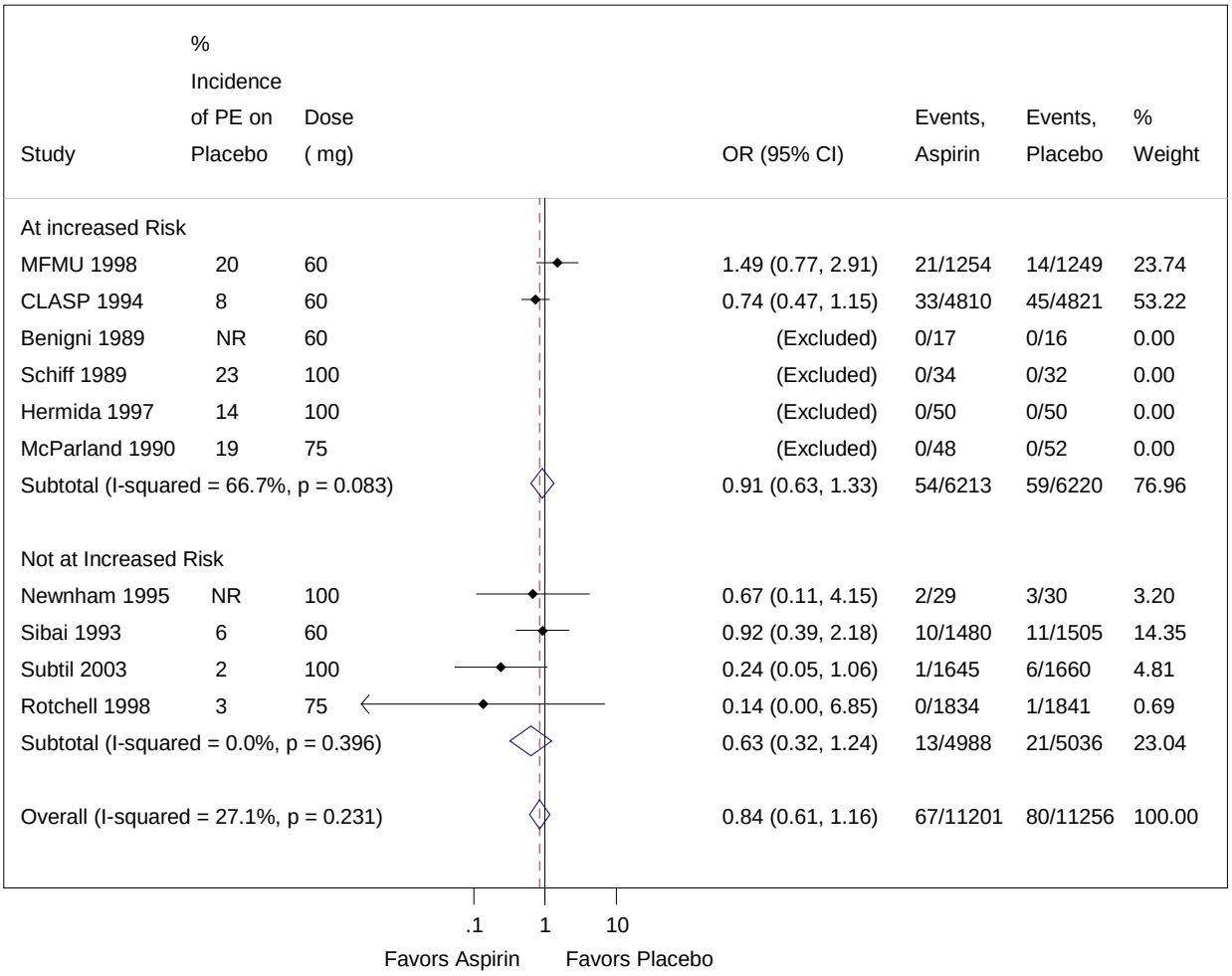


Figure 7. Pooled Analysis of Cesarean Delivery Sorted by Sample Size (Trials of Women at Risk of Preeclampsia)

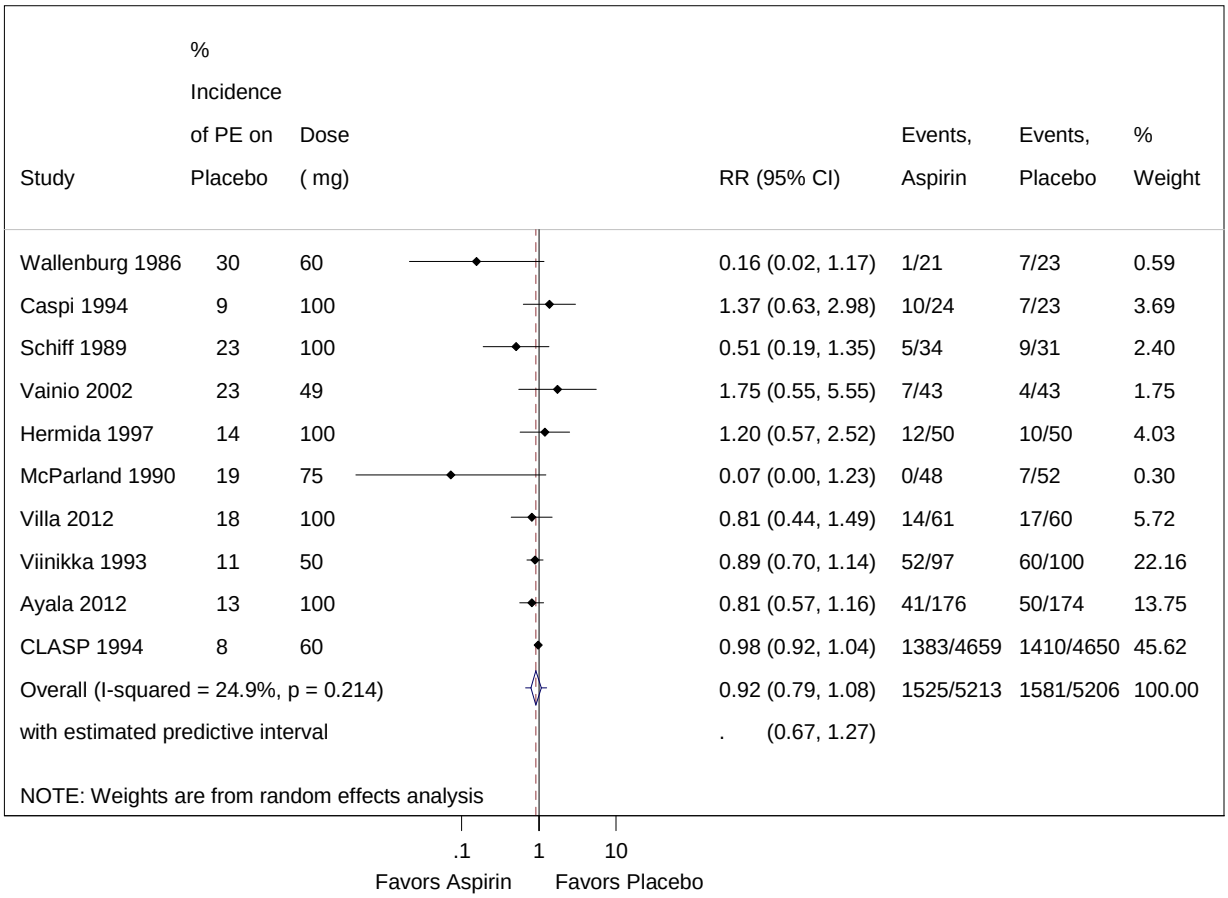


Figure 8. Pooled Analysis of Mean Birth Weight Sorted by Sample Size (Trials of Women at Risk of Preeclampsia)

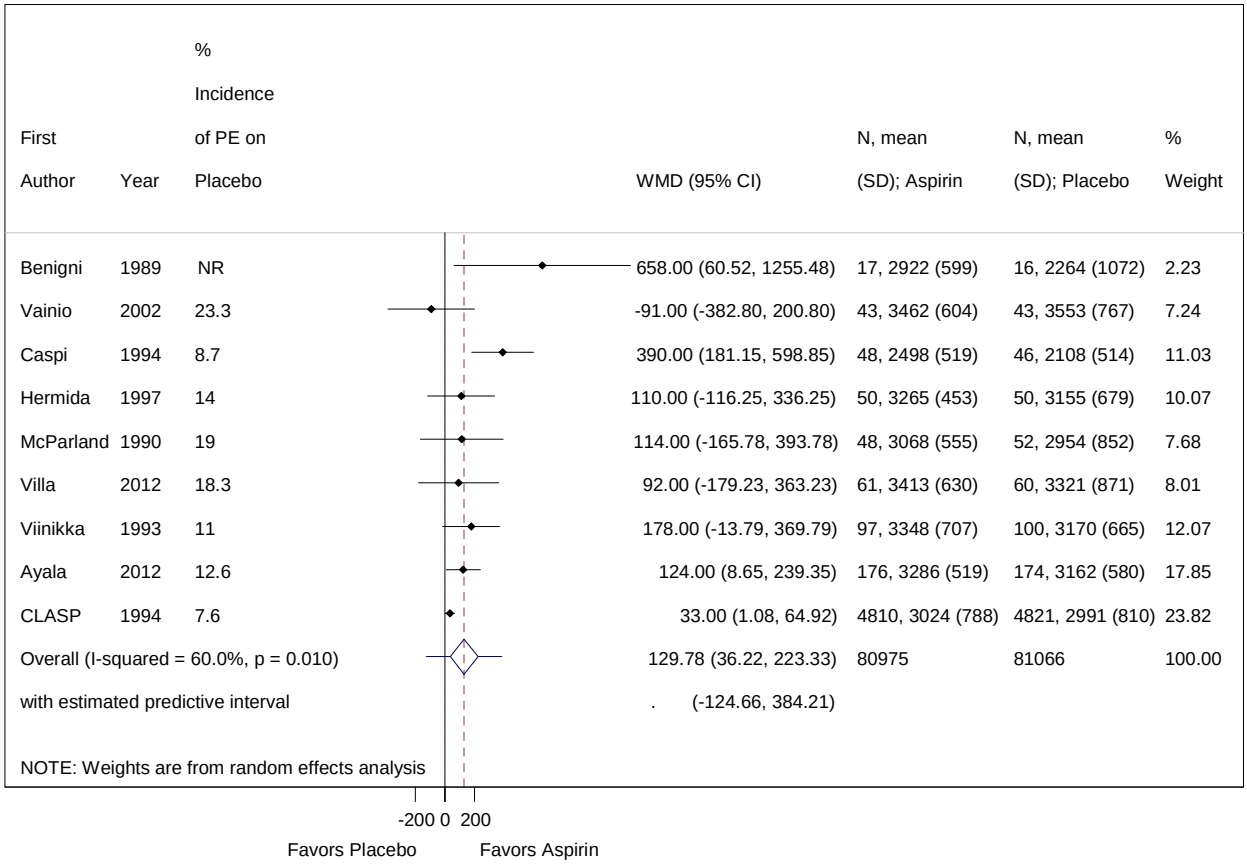


Figure 9. Pooled Analysis of Abruption Sorted by Sample Size (All Trials)

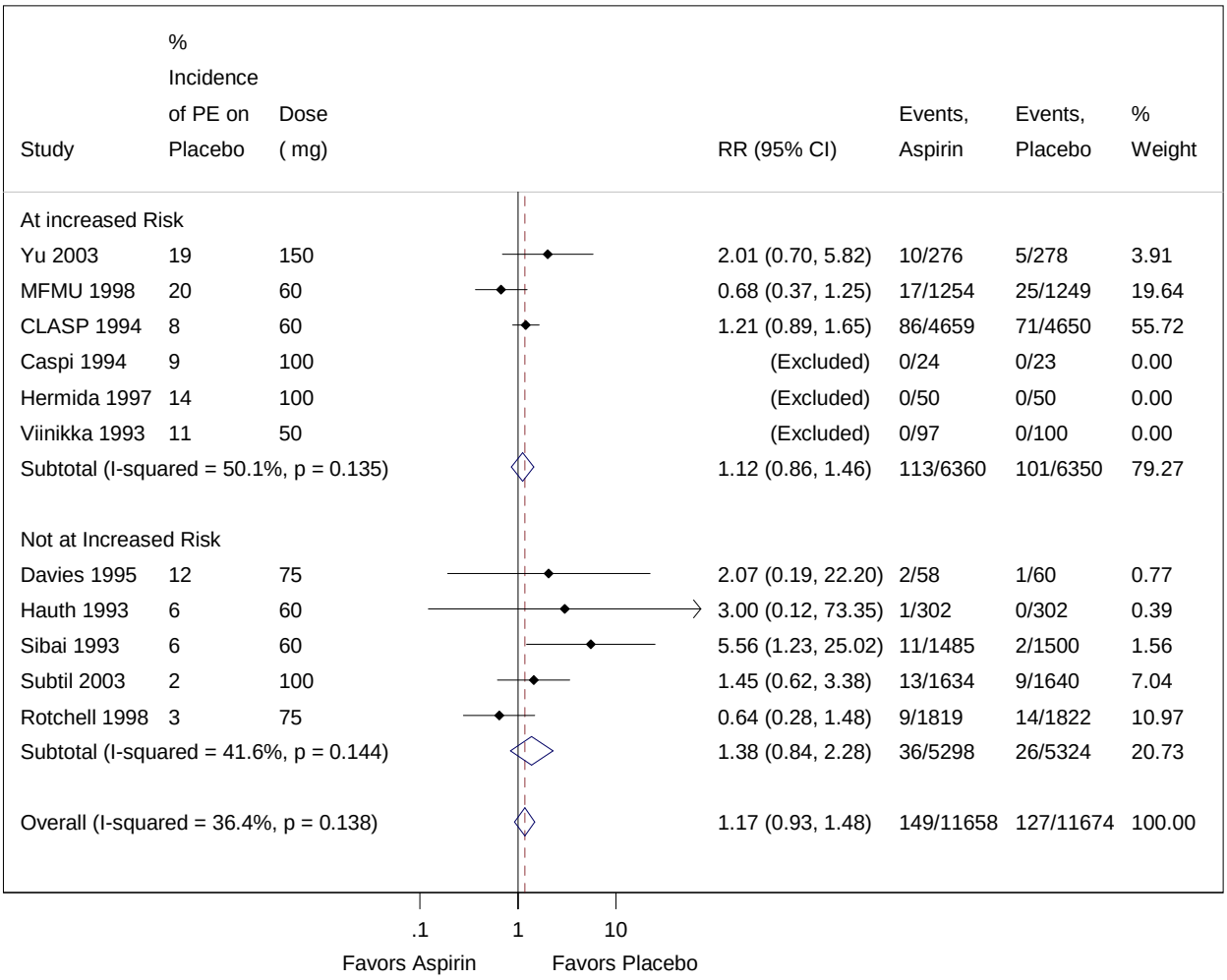


Figure 10. Pooled Analysis of Postpartum Hemorrhage Sorted by Sample Size (All Trials)

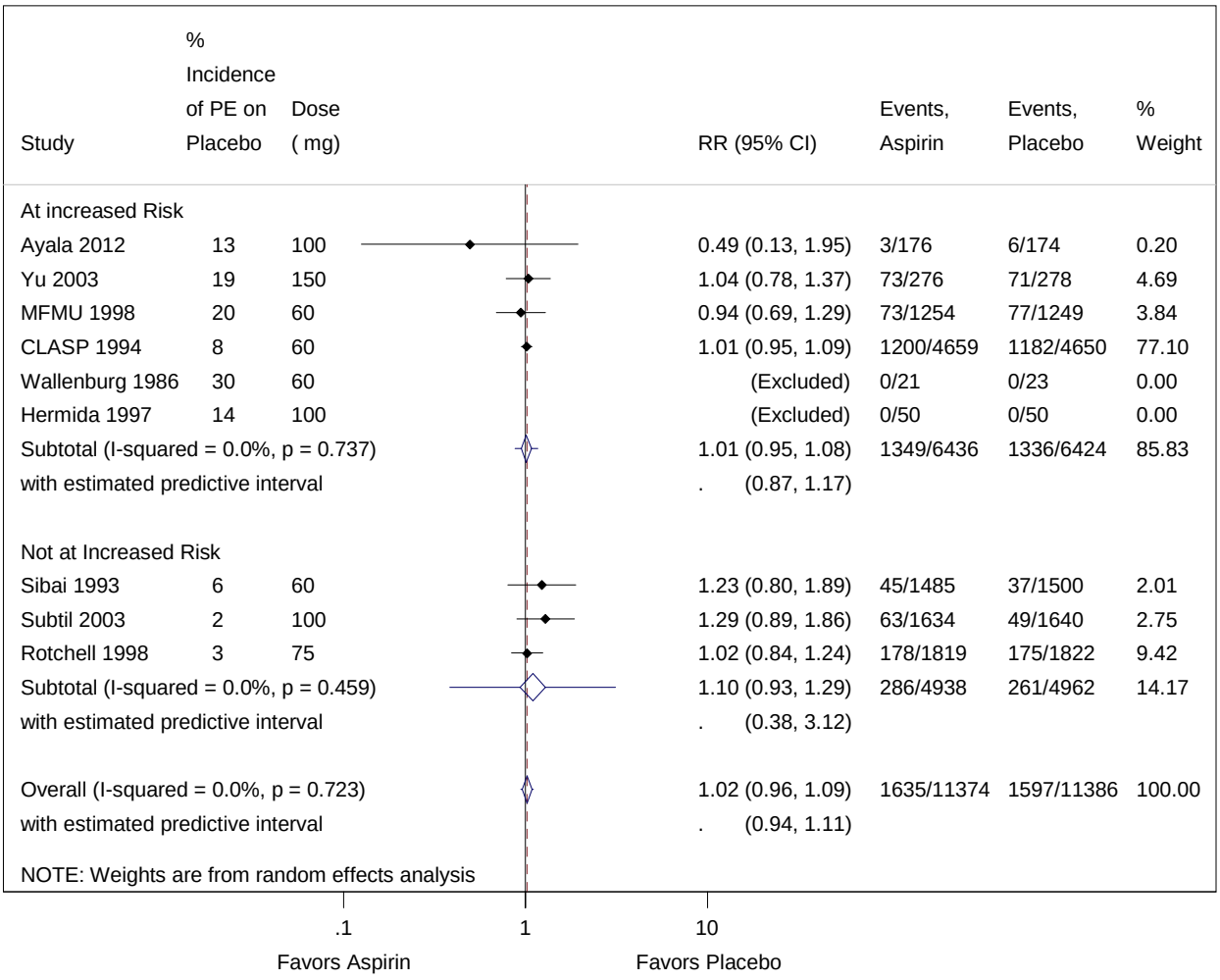


Table 1. Current Clinical Recommendations

Organization	Guideline	Definition of treatment population
National Institute for Health and Clinical Excellence (NICE), 2011	NICE advises that women at high risk of preeclampsia or with more than one moderate risk factor take 75 mg of aspirin daily from 12 weeks until the birth of the baby.	*High risk if any:* • Hypertensive disease during prior pregnancy • Chronic kidney disease • Autoimmune disease • Type 1 or type 2 diabetes • Chronic hypertension *High risk if >1 of the following moderate risks:* • First pregnancy • Age ≥40 years • >10-year pregnancy interval • BMI ≥35 kg/m^2 • Family history of preeclampsia (mother, sister) • Multiple pregnancy
World Health Organization (WHO), 2011	WHO recommends that women at high risk of preeclampsia take 75 mg of aspirin daily, initiated before 20 weeks of pregnancy.	*High risk:** • Previous preeclampsia • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multiple pregnancy

*The WHO guidelines note that this is not an exhaustive list of high-risk factors.

Table 2. Preeclampsia and Maternal Health Outcomes in Studies of Aspirin Prophylaxis in Pregnant Women

Study, Year Quality	Treatment group	N Analyzed	Preeclampsia incidence, n (%)	Organ/system injury or failure, n (%)	Cesarean delivery, n (%)	Mortality, n (%)
Ayala, 2012[59] Good	IG	176	11 (6.3)	NR	41 (23.3)*	NR
	CG	174	22 (12.6)	NR	50 (28.7)*	NR
Caspi, 1994[61] Good	IG	24	0 (0)	NR	10 (41.7)	NR
	CG	23	2 (8.7)	NR	7 (24.0)	NR
CLASP, 1994[58] Good	IG	4,659†	267 (6.7)	*Eclampsia:* 7 (0.2)	*Prelabor Cesarean:* IG: 1,007 (21.6) *Intrapartum Cesarean:* IG: 376 (8.1)	1 (0.02)
	CG	4,650†	302 (7.6)	*Eclampsia:* 7 (0.2)	*Prelabor Cesarean:* IG: 987 (21.2) *Intrapartum Cesarean:* IG: 423 (9.1)	0 (0)
Gallery, 1997[62] Fair	IG	58	NR	NR	NR	0 (0)
	CG	50	NR	NR	NR	0 (0)
Hermida, 1997[64] Good	IG	50	3 (6.0)	NR	12 (24.0)	NR
	CG	50	7 (14.0)	NR	10 (20.0)	NR
McParland, 1990[65] Fair	IG	48	1 (2.1)	NR	0 (0)	NR
	CG	52	10 (19.2)	NR	7 (13.5)	NR
MFMU, 1998[57] Good	IG	1,254	226 (18.0)	NR	NR	NR
	CG	1,249	250 (20.0)	NR	NR	NR
Schiff, 1989[66] Good	IG	34	1 (2.9)§	NR	5 (14.7)	NR
	CG	31	7(22.6)	NR	9 (29.0)	NR
Vainio, 2002[67] Fair	IG	43	2 (4.7)	NR	7 (16.3)	0 (0)
	CG	43	10 (23.3)	NR	4 (9.3)	0 (0)
Viinikka, 1993[68] Fair	IG	97	9 (9.3)	NR	52 (53.6)‡	NR
	CG	100	11 (11.0)	NR	60 (60)‡	NR
Villa, 2012[69] Fair	IG	61	8 (13.1)	*HELLP Syndrome:* 0 (0)	*Cesarean delivery during labor:* 11 (18.0) *Elective Cesarean:* 3 (4.9)	0 (0)
	CG	60	11 (18.3)	*HELLP Syndrome:* 1 (0.02)	*Cesarean delivery during labor:* 14 (23.3) *Elective Cesarean:* 3 (5.0)	0 (0)
Wallenburg, 1986[70] Good	IG	21	0 (0)	*Eclampsia:* 0 (0)	1 (4.8)	0 (0)
	CG	23	7 (30.0)	*Eclampsia:* 1 (4.3)	7 (30.4)	0 (0)
Yu, 2003[71] Good	IG	276	49 (17.8)	NR	NR	NR
	CG	278	52 (18.7)	NR	NR	NR

* Calculated.
† All pregnancies with data.
‡ Reported as "induction or elective cesarean section."
§ $p<0.05$ compared with CG.

Abbreviations: CG = control group; CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; HELLP = hemolysis, elevated liver enzymes, low platelet count; IG = intervention group, NA = not applicable; NR = not reported.

Table 3. Fetal Health Outcomes in Studies of Aspirin Prophylaxis in Pregnant Women

Study, Year Quality	Treatment group	N Analyzed	Preterm birth (<37 weeks), n (%)	Mean (SD) birth weight, g	IUGR/SGA, n (%)	Complications, n (%)	Perinatal/neonatal mortality, n (%)
Ayala, 2012[59] Good	IG	176	7 (4.0)*	3,286 (519)	16 (9.1)*†	NR	2 (1.1)*
	CG	174	20 (11.5)*	3,162 (580)	32 (18.4)*†	NR	5 (2.9)*
Benigni, 1989[60] Fair	IG	17	2 (11.8)	2,922 (599)	2 (11.8)†	*Ventilation:* 0 (0)	0 (0)
	CG	16	5 (31.3)	2264 (1072)	6 (37.5)†	*Ventilation:* 3 (18.8)	1 (6.3)
Caspi, 1994[61] Good	IG	48	11 (46.0)§	*1st twin:* 2,506 (623) *2nd twin:* 2,499 (504) *Both twins:* 4,996 (1,038)	6 (12.5)‡	NR	2 (4.2)
	CG	46	14 (61)‖	*1st twin:* 2,204 (533) *2nd twin:* 2,011 (546) *Both twins:* 4,215 (1,027)	11 (23.9)‡	NR	2 (4.3)
CLASP, 1994[58]¶ Good	IG	4,810	686 (17.2)	3,024 (788)	244 (5.9)#	*Induced delivery:* 1,460 (31.3)	77 (1.9)
	CG	4,821	761 (19.1)	2,991 (810)	272 (6.6)#	*Induced delivery:* 1,406 (30.2)	97 (2.3)
Gallery, 1997[62] Fair	IG	58	6 (11)*	3,292 (2,978–3,521)**‡‡	NR	NR	4 (6.9)
	CG	50	8 (16)*	3,090 (2,621–3,511)**	NR	NR	2 (4.0)
Grab, 2000[63] Fair	IG	22	NR	3,150 (560–3,770)††	NR	NR	NR
	CG	21	NR	2,900 (800–4,070)††	NR	NR	NR
Hermida, 1997[64] Good	IG	50	1 (2.0)	3,265 (64)	1 (2.0)†	NR	0 (0)
	CG	50	5 (10.0)	3,155 (96)	2 (4.0)†	NR	0 (0)
McParland, 1990[65] Fair	IG	48	NR	3068 (555)	7 (14.0)##	NR	1 (2.1)*§§
	CG	52	NR	2954 (852)	7 (14.0)##	NR	3 (5.8)*§§
MFMU, 1998[57] Good	IG	1,254	502 (40)*	NR	129 (10)*‡	NR	43 (3.0)*
	CG	1,249	537 (43)*	NR	108 (9)*‡	NR	56 (5.0)*
Schiff, 1989[66] Good	IG	34	2 (5.9)*	3,037 (NR)	2 (5.9)‡	*Admitted to NICU:* 2 (5.9) *Ventilary support needed:* 1 (2.9)	0 (0)
	CG	32	6 (18.8)*	2,706 (NR)‖ ‖	6 (19.4)‡‖ ‖	*Admitted to NICU:* 7 (21.9) *Ventilary support needed:* 3 (9.4)	0 (0)
Vainio, 2002[67] Fair	IG	43	NR	3,462 (604)	1 (2.3)†	NR	0 (0)
	CG	43	NR	3,553 (767)	3 (7.0)†	NR	0 (0)
Viinikka, 1993[68] Fair	IG	97	NR	3,348 (707)	4 (4.1)¶¶	NR	2 (2.1)
	CG	100	NR	3,170 (665)	9 (9.0)¶¶	NR	0 (0)
Villa, 2012[69] Fair	IG	61	NR	3,413 (630)	2 (3.3)¶¶	*Umbilical artery pH <7.15:* 7 (12.5)	3 (4.9)*
	CG	60	NR	3,321 (871)	6 (10.0)¶¶	*Umbilical artery pH <7.15:* 4 (7.4)	1 (1.7)*
Wallenburg, 1986[70] Good	IG	21	0 (0)	3,190 (2,380-4,320)†††	4 (19.0)†	NR	1 (4.8)
	CG	23	4 (17.3)	3,040 (530-4,035)†††	6 (26.0)†	NR	1 (4.3)
Yu, 2003[71] Good	IG	276	67 (24.3)	NR	61 (22.1)##	NR	7 (2.5)
	CG	278	75 (27.0)	NR	68 (24.4)##	NR	4 (1.4)

* Calculated.
† IUGR not defined.
‡ IUGR defined as birth weight <10th percentile.
§ N is the number of mothers (n=24).
‖ N is the number of mothers (n=23).

Table 3. Fetal Health Outcomes in Studies of Aspirin Prophylaxis in Pregnant Women

¶ N analyzed represents all fetal outcomes; data presented for preterm birth are for study subjects entered for prophylaxis (IG: n=3,992; CG: n=3,982); data presented for IUGR/SGA and perinatal/neonatal mortality are for study subjects entered for prophylaxis (IG: n=4,123; CG: n=4,134); data presented for complications are for all pregnancies with data (IG: n=4,659; CG: n=4,650).
** Median (range).
†† Mean (range).
‡‡ These data were calculated without the four intrauterine deaths, as the extent of postmortem weight alteration could not be assessed (n=54).
§§ The one death in the IG was due to a cord accident at delivery, whereas the three in the CG were due to hypertension complications.
‖ ‖ N=31 (twins not counted individually for these outcomes).
¶¶ SGA defined as birth weight <2 SDs.
IUGR defined as birth weight <5th percentile.

Abbreviations: CG = control group; CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; IG = intervention group; IUGR = intrauterine growth restriction; NICU = neonatal intensive care unit; NR = not reported, SD = standard deviation; SGA = small for gestational age.

Table 4. Adverse Events Reported in Included RCTs of Aspirin Therapy in Pregnant Women

Study, Year Quality	Treatment group	N Analyzed	Perinatal Mortality (n, %)	Abruptio placentae, n (%)	Intracranial fetal bleeding, n (%)	Postpartum hemorrhage, n (%)	Mean (SD) EBL, ml	Other, n (%)
Ayala, 2012[59] Good	IG	176	2 (1.1)*	NR	NR	3 (1.7)*	NR	*Gestational HTN, % likely (95% CI):* 14.8 (9.5 to 20.0) *Antepartum hemorrhage:* 6 (3.4)*
	CG	174	5 (2.9)*	NR	NR	6 (3.4)*	NR	*Gestational HTN, % likely (95% CI):* 28.2 (21.5 to 34.8) *Antepartum hemorrhage:* 9 (5.2)*
Benigni, 1989[60] Fair	IG	17	0	NR	0 (0)	NR	400 (183)	NR
	CG	16	1 (6.3)	NR	0 (0)	NR	475 (185)	NR
Caspi, 1994[61] Good	IG	24	2 (8.3)	0 (0)	NR	NR†	NR†	NR
	CG	23	2 (8.7)	0 (0)	NR	NR	NR	NR
CLASP, 1994[58] Good	IG	*Mothers:* 4,659 *Infants:* 4,810	129 (2.7)	86 (1.8)	*Intraventricular hemorrhage:* 33 (0.7)	*Postpartum bleed ≥500 mL:* 1,200 (25.8)	NR	*Transfusion:* 188 (4.0) *Special care admission:* 946 (19.7)
	CG	*Mothers:* 4,650 *Infants:* 4,821	136 (2.8)	71 (1.5)	*Intraventricular hemorrhage:* 45 (0.9)	*Postpartum bleed ≥500 mL:* 1,182 (25.4)	NR	*Transfusion:* 147 (3.2) *Special care admission:* 1,016 (21.1)
CLASP, 1994[58] Good 18 month followup	IG	2,146	NR	NR	NR	NR	NR	*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	NR	NR	NR	NR	NR	*Gross motor failure:* 10 (0.5) *Fine motor failure:* 39 (1.8) *Height <3rd percentile:* 248 (11.2) *Weight <3rd percentile:* 129 (5.8)
Davies, 1995[76] Fair	IG	58	0	2 (3.4)	NR	NR	NR	*Admission to NICU:* IG: 1 (1.7)
	CG	60	0	1 (1.6)	NR	NR	NR	*Admission to NICU:* CG: 2 (3.3)
Gallery, 1997[62] Fair	IG	58	4 (7)	NR	NR	NR	NR	3 of the 4 perinatal deaths were preceded by antepartum hemorrhage
	CG	50	2 (4)	NR	NR	NR	NR	1 of the 2 perinatal deaths was preceded by antepartum hemorrhage
Hauth, 1993[73] Good	IG	302	1 (0.3)	1 (0.3)	NR	NR	NR	NR
	CG	302	1 (0.3)	0 (0)	NR	NR	NR	NR
Hermida, 1997[64] Good	IG	50	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
	CG	50	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR
McParland, 1990[65] Fair	IG	48	1 (2.1)*‡	NR	0 (0)	NR	289 (188)	NR
	CG	52	3 (5.8)*‡	NR	0 (0)	NR	358 (228)	NR
MFMU, 1998[57] Good	IG	1,254	43 (3.0)	17 (1)*	*Neonatal intraventricular hemorrhage:* 25 (2)*	73 (6)*	NR	NR

Table 4. Adverse Events Reported in Included RCTs of Aspirin Therapy in Pregnant Women

Study, Year Quality	Treatment group	N Analyzed	Perinatal Mortality (n, %)	Abruptio placentae, n (%)	Intracranial fetal bleeding, n (%)	Postpartum hemorrhage, n (%)	Mean (SD) EBL, ml	Other, n (%)
	CG	1,249	56 (5.0)	25 (2)*	*Neonatal intraventricular hemorrhage:* 12 (1)*	77 (6)*	NR	NR
Newnham, 1995[79] Good	IG	*Infants:* 29	NR	NR	*Intraventricular hemorrhage:* 2 (6.9)	NR	NR	*Admission to NICU:* 13 (44.8)
	CG	*Infants:* 30	NR	NR	*Intraventricular hemorrhage:* 3 (10.0)	NR	NR	*Admission to NICU:* 7 (23.3)
Rotchell, 1998[75] Good	IG	*Mothers:* 1,819 *Infants:* 1,834	15 (0.8)*	9 (0.5)	*Intraventricular hemorrhage:* 0 (0)	178 (9.8)	NR	*Fetal bleeding problems:* IG: 9 (0.5) *Other antepartum bleed:* IG: 65 (3.6) *Bleed (amount not known):* IG: 173 (9.5) *Transfusion:* IG: 19 (1.0) *Admission to special care nursery:* IG: 272 (15.3)
	CG	*Mothers:* 1,822 *Infants:* 1,841	11 (0.6)*	14 (0.8)	*Intraventricular hemorrhage:* 1 (0.1)	175 (9.6)	NR	*Fetal bleeding problems:* CG: 9 (0.5) *Other antepartum bleed:* CG: 76 (4.2) *Bleed (amount not known):* CG: 188 (10.3) *Transfusion:* CG: 18 (1.0) *Admission to special care nursery:* CG: 293 (16.5)
Schiff, 1989[66] Good	IG	34	0	NR	*Intraventricular hemorrhage:* 0 (0)	NR	NR	*Cephalhematoma:* 0 (0)
	CG	32	0	NR	*Intraventricular hemorrhage:* 0 (0)	NR	NR	*Cephalhematoma:* 1 (3.1)
Sibai, 1993[72] Good	IG	*Mothers:* 1,485 *Infants:* 1,505	30 (2.0)	11 (0.7)	*Cerebral hemorrhage:* 10 (0.7)§	45 (3.0)	405 (215)‖	*Cephalohematoma:* 68 (4.6) *Any neonatal bleeding disorder:* 104 (7.0) *Admission to NICU:* 132 (8.8) *Blood transfusion required:* *Mother:* 7 (0.5) *Infant:* 19 (1.3)

Table 4. Adverse Events Reported in Included RCTs of Aspirin Therapy in Pregnant Women

Study, Year Quality	Treatment group	N Analyzed	Perinatal Mortality (n, %)	Abruptio placentae, n (%)	Intracranial fetal bleeding, n (%)	Postpartum hemorrhage, n (%)	Mean (SD) EBL, ml	Other, n (%)
	CG	*Mothers:* 1,500 *Infants:* 1,519	21 (1.4)	2 (0.1)**	*Cerebral hemorrhage:* 11 (0.7)§	37 (2.5)	404 (152)‖	*Cephalohematoma:* 55 (3.7) *Any neonatal bleeding disorder:* 98 (6.5) *Admission to NICU:* 142 (9.3) *Blood transfusion required:* *Mother:* 10 (0.7) *Infant:* 20 (1.3)
Subtil, 2003[74] Good	IG	*Mothers:* 1,634 *Infants:* 1,645	12 (0.7)	13 (0.8)	1 (0.06)	63 (3.9)	NR	*Major hemorrhage in baby:* 2 (0.1) *Transfer to NICU:* 116 (7.1)
	CG	*Mothers:* 1,640 *Infants:* 1,660	11 (0.7)	9 (0.5)	6 (0.4)	49 (3.0)	NR	*Major hemorrhage in infant:* 2 (0.1) *Transfer to NICU:* 111 (6.7)
Vainio, 2002[67] Fair	IG	43	0	NR	NR	NR	300 [250–450]¶	NR
	CG	43	0	NR	NR	NR	350 [250–450]¶	NR
Viinikka, 1993[68] Fair	IG	97	2 (2.1)	0 (0)	NR	NR	353 (100–2,500)#	*Admitted to NICU:* 10 (10.3)
	CG	100	0 (0)	0 (0)	NR	NR	346 (50–6,750)#	*Admitted to NICU:* 21 (21)
Villa, 2012[69] Fair	IG	61	NR	NR	NR	NR	NR	*Miscarriage:* 3 (3.9)
	CG	60	NR	NR	NR	NR	NR	*Miscarriage:* 1 (1.3)
Wallenburg, 1986[70] Good	IG	21	1 (4.8)	1 suspected (but could not be confirmed)	NR	0 (0)	NR	NR
	CG	23	1 (4.3)	0	NR	0 (0)	NR	NR
Yu 2003[71] Good	IG	276	7 (2.5)	10 (3.6)	NR	73 (26.4)	NR	*Blood transfusion:* 6 (2.2)
	CG	278	4 (1.4)	5 (1.8)	NR	71 (25.5)	NR	*Blood transfusion:* 7 (2.5)

* Calculated n of events.
† Authors state that "no excessive bleeding was encountered…in the ASA group."
‡ 1 death in the IG was due to a cord accident at delivery, whereas the 3 in the CG were due to hypertension complications.
§ Denominators used in these calculations exclude 25 spontaneous abortions and fetal deaths in the aspirin group and 14 in the placebo group (IG: n=1,480; CG: n=1,505).
‖ Estimated blood loss from vaginal deliveries only (IG: n=1,156; CG: n=1,160).
¶ Reported as blood loss at delivery (mL), median [lower and upper quartile].
# Reported as "bleeding during delivery," mean mL (range).
** p=0.01.

Abbreviations: CG = control group; CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; EBL = estimated blood loss; IG = intervention group; NR = not reported; NICU = neonatal intensive care unit; SD = standard deviation.

Table 5. Adverse Events Reported in Included Observational Studies of Aspirin Therapy in Pregnant Women

Study, Year Quality	Study design	N Analyzed	Perinatal Mortality (n, %)	Abruptio placentae, n (%)	Intracranial fetal bleeding, n (%)	Postpartum hemorrhage, n (%)	Mean (SD) EBL, ml	Other, n (%)
Jensen, 2010[77] Good	Retrospective cohort	47,400	NR	NR	NR	NR	NR	*Cryptorchidism:* n, adjusted HR (95% CI) *Unexposed*: 904 (reference) *Exposed*: 76, 1.18 (0.93 to 1.49) *Orchiopexy*: n, adjusted HR (95% CI) *Unexposed*: 522 (reference) *Exposed*: 43, 1.15 (0.84 to 1.56)
Keim, 2006[78] Good	Case-control of previously collected data	*Cases*: 542 *Controls*: 2,587	NR	NR	NR	NR	NR	*Miscarriage**: *Cases*: *No Aspirin*: 383 (71) *Aspirin*:159 (29) *Controls:* *No Aspirin*:1,711 (66) *Aspirin*: 876 (34)

* Aspirin use anytime during pregnancy.

Abbreviations: EBL = estimated blood loss; NR = not reported; SD = standard deviation.

Table 6. Summary of Evidence for Benefits and Harms of Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia

Key Question(s)	# of Studies (k)	Design	Major Limitations	Consistency	Applicability	Overall Evidence	Summary of Findings
KQ1. Is there evidence that aspirin reduces adverse health outcomes in women at increased risk for preeclampsia? KQ1a. Does low-dose aspirin reduce maternal morbidity or mortality?	Maternal mortality k=5 n=9,668	RCT	Only 1 event in all studies combined; insufficient power to determine effect.	Cannot determine	Applicable to U.S. prenatal and hospital settings.	2 good, 3 fair Overall: Insufficient	1 maternal death recorded in the aspirin group of the largest study (CLASP), occurring 2 days after delivery from pulmonary embolus.
	Eclampsia, HELLP, organ/system damage or failure k=3 n=9,474	RCT	Insufficient power to determine effect, outcomes not often or consistently reported.	Cannot determine	Applicable to U.S. prenatal and hospital settings.	2 good, 1 fair Overall: Insufficient	7 aspirin-allocated and 7 placebo-allocated cases of eclampsia were reported in the largest study, and 1 case of eclampsia reported in the control group of 1 small study. There was 1 case of HELLP syndrome in a study of 121 subjects.
	Cesarean delivery k=10 n=10,419	RCT	Most studies did not distinguish between elective Cesarean delivery vs. Cesarean delivery during labor.	Low heterogeneity (I^2=24.9%; p=0.21). 7 out of 10 studies had results in the direction of reduced risk.	Good applicability. Studies all conducted outside the U.S., but applicable to U.S. prenatal and hospital health care settings.	6 good, 4 fair Overall: Good	No difference in the rate of Cesarean delivery was observed (pooled RR, 0.92 [95% CI, 0.79 to 1.08]).
KQ1b. Is there evidence that aspirin reduces perinatal/fetal morbidity or mortality in women at increased risk for preeclampsia?	Perinatal mortality k=13 n=12,492	RCT	The pooled analysis (k=10; n=12,240) had insufficient power to detect a modest effect of aspirin on perinatal mortality. A meta-analysis sample size of n=31,504 would be needed to obtain 80% power to detect an 18% reduction in perinatal mortality.	Most studies (13/15) reported perinatal mortality. 10 could be pooled as 3 had no events. High consistency (overall I^2=0%; p=0.78). The 2 largest studies (n=10,760) had consistent effects tending in the direction of an aspirin benefit.	Good applicability. Studies primarily conducted outside the U.S., but 1 large study based in the U.S. is included. The evidence does not offer guidance on the best method for identifying patients who would most benefit from prophylaxis.	8 good, 5 fair Overall: Good	Given limited power, meta-analysis results cannot eliminate a reduced risk of perinatal mortality in women at elevated preeclampsia risk (pooled RR,* 0.81 [95% CI, 0.65 to 1.01]).
	Preterm birth (<37 weeks) k=10 n=11,779	RCT	The effect sizes are smaller in larger studies, and there was evidence of significant small study effects, possibly indicating publication	10/15 studies reported this outcome. Very good consistency, with all included trials showing effects in the same direction.	Good applicability. Most studies conducted outside the U.S., but applicable to U.S. prenatal and hospital	8 good, 2 fair Overall: Fair to good	There was evidence that aspirin reduced the risk of preterm birth (pooled RR, 0.86 [95% CI, 0.76 to 0.98]) in women at elevated risk for preeclampsia. The magnitude of estimated

Table 6. Summary of Evidence for Benefits and Harms of Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia

Key Question(s)	# of Studies (k)	Design	Major Limitations	Consistency	Applicability	Overall Evidence	Summary of Findings
			bias. Inability to disentangle the confounding of study size and other study characteristics of interest in stratified analyses.	Low to moderate heterogeneity (I^2=33.2%; p=0.14).	health care settings. Different management of labor across settings likely affect the outcome, but not differentially by experimental group. The body of evidence does not offer guidance on the best method for identifying patients who would most benefit from prophylaxis.		benefit could be exaggerated by small study effects.
	IUGR/SGA k=13 n=12,504	RCT	Inconsistent definition of IUGR/SGA ranging from <3rd to <10th percentile birth weight for gestational age (<10th percentile most common). The effect sizes are smaller in larger studies, and there was evidence of small study effects, possibly indicating publication bias. Diverse inclusion criteria were used and preeclampsia incidence varied widely across studies (8% to 30%).	13/15 studies reported usable data for this outcome, eliminating only 151 patients. Low to moderate heterogeneity (I^2=36.9%; p=0.09) All but 1 trial, the large multisite trial conducted in the U.S., reported effects in the same direction.	Good applicability. Most studies were conducted outside the U.S., but applicable to U.S. prenatal and hospital health care settings. The body of evidence does not offer guidance on the best method for identifying patients who would most benefit from prophylaxis.	8 good, 5 fair Overall: Fair to good	There was evidence of a reduction in IUGR with aspirin (pooled RR, 0.80 [95% CI, 0.65 to 0.99]) in women at elevated risk for preeclampsia. The magnitude of estimated benefit could be exaggerated by small study effects
	Birth weight k=13 n=10,968	RCT	The effect sizes are smaller in larger studies, and there was evidence of small study effects, possibly indicating publication bias.	Moderate heterogeneity (I^2=60.0%; p=0.01). All except 1 small trial (n=86) reported effects in the same direction, favoring aspirin. Pooled estimates were not precise.	Fair applicability. This outcome was not reported in the largest U.S.-based trial. Most studies were conducted outside the U.S., but applicable to U.S. prenatal and hospital	6 good, 7 fair Overall: Fair	Aspirin increased the mean birth weight of infants by a pooled weighted mean difference of 129.8 g (95% CI, 36.2 to 223.3; n=10,712)† This could reflect extension of length of gestation or reduction in IUGR, and would be consistent with a

Table 6. Summary of Evidence for Benefits and Harms of Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia

Key Question(s)	# of Studies (k)	Design	Major Limitations	Consistency	Applicability	Overall Evidence	Summary of Findings
					health care settings. The body of evidence does not offer guidance on the best method for identifying patients who would most benefit from prophylaxis.		possible benefit in perinatal mortality. Estimated effect is not precise and may be exaggerated due to small study effects.
KQ2. Is there evidence that aspirin prevents preeclampsia in women at increased risk for preeclampsia?	Preeclampsia k=13 n=12,184	RCT	Minor variations in the definition of preeclampsia used, especially the cutpoints used to diagnose proteinurea. Evidence of small study effects, possibly indicating publication bias. It is not possible to determine whether lower aspirin dosage might account for smaller effects observed in the 2 large trials. Diverse inclusion criteria were used and preeclampsia incidence varies widely (8% to 30%).	Except for 1 small trial (n=43), all studies reported effects in the same direction. The effect sizes and confidence intervals in the 2 largest studies are nearly identical. There is moderate heterogeneity (I^2=40.5; p=0.06).	Good applicability. Most studies were conducted outside the U.S., but applicable to U.S. prenatal and hospital health care settings. The evidence does not offer guidance on the best method for identifying patients who would most benefit from prophylaxis.	8 good, 5 fair Overall: Good	There is evidence of a modest reduction in preeclampsia for women at risk who take low-dose aspirin during pregnancy. Aspirin significantly reduces the risk of preeclampsia, by nearly a quarter when all included studies are pooled (RR, 0.76 [95% CI, 0.62 to 0.95]). Effect estimates could be overestimated due to small study effects. Although study-level results were not statistically significant, the 2 largest trials both estimated a 10% reduction in risk of preeclampsia; this estimate is consistent with the pooled result, but more conservative.
KQ3. What are the harms of aspirin use during pregnancy? (Includes trials of pregnant women not at elevated risk of preeclampsia) KQ3a. Are there harms to the	Perinatal mortality *Elevated preeclampsia risk* k=13 n=12,492 *Low preeclampsia risk*	RCT	The pooled analysis for women in all risk groups had insufficient power to detect a modest beneficial or harmful effect of aspirin on the risk of perinatal mortality. Appropriately stratifying by risk of preeclampsia (increased vs. not increased) reduced	Very low heterogeneity (I^2=0%; p=0.65), but because the outcome is rare, small studies are inconsistent in the direction of effect. There was a significant interaction between elevated risk and low-risk trials and perinatal mortality.	Good applicability. Evidence on the outcome are from RCTs of women at elevated risk of preeclampsia taking low-dose aspirin, and women not at elevated risk taking low-dose aspirin. Most studies were	12 good, 6 fair Overall: Good	An increase in the risk of perinatal mortality cannot be ruled out in pooled analysis of women at both elevated and low risk (RR,* 0.91 [95% CI, 0.75 to 1.11]; n=22,848). However, when the pooled analysis was stratified by risk, summary effects were in opposite directions (toward increased perinatal

Table 6. Summary of Evidence for Benefits and Harms of Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia

Key Question(s)	# of Studies (k)	Design	Major Limitations	Consistency	Applicability	Overall Evidence	Summary of Findings
woman or fetus/offspring from aspirin use during pregnancy?	k=5 n=10,726 Total n=23,218		power further.	In the 2 large trials with women at elevated risk, results were toward benefit. In the 3 large trials with women at low risk, results were in the direction of harm. Stratified analyses showed opposite directions of effect (further risk reduction in those at increased risk and increased risk on those not at increased risk), but were not powered adequately.	conducted outside the U.S., but would likely be similar to U.S. prenatal and hospital health care settings.		risk in aspirin-using women at low risk and toward reduced perinatal mortality risk in aspirin-using women at elevated risk); thus, perinatal mortality was less of a concern after stratified analysis in those at elevated risk (RR,* 0.81 [95% CI, 0.65 to 1.01]; n=12,240). Possible increased risk of perinatal mortality in low-risk women with use of aspirin (RR,* 1.33 [95% CI, 0.90 to 1.96]; n=10,608) suggests caution.
	Abruptio placentae *Elevated preeclampsia risk* k=6 n=12,710 *Low preeclampsia risk* k=5 n=10,622 Total n=23,332	RCT	Less than half (6/15) of elevated risk trials reported this outcome, and among these 3 had no abruption events. Severely underpowered analyses with potential publication bias in trials assessing women at elevated risk. Even when pooling trials in both low- and elevated-risk women (k=11; n=23,332) there was insufficient power. For the observed n and event rates, the pooled analysis had only 27% power; a sample size over 100,000 would be required to detect a 20% difference in abruption rates with 80% power. The study with the largest RR, indicating harm from aspirin, acknowledged that the abruption rate in	3 trials reported no abruption events (all trials of women at elevated risk), 6 (2 in women at elevated risk; 4 in low-risk women) reported more events in the aspirin group, and 2 (1 elevated risk; 1 low risk) reported more events in the control arm. The 2 large trials in women with elevated risk (MFMU, CLASP) found inconsistent effects. Heterogeneity was low to moderate (I^2=36.4; p=0.14).	Good applicability. Evidence on the outcome are from RCTs of women at elevated risk of preeclampsia taking low-dose aspirin, and women not at elevated risk taking low-dose aspirin. Most studies were conducted outside the U.S., but applicable to U.S. prenatal and hospital health care settings.	9 good, 2 fair Overall: Fair to good	Given power limitations and small study effects, an increase in the risk of placental abruption for women taking low-dose aspirin during pregnancy cannot be ruled out (pooled RR,* 1.19 [95% CI, 0.81 to 1.76]; n=22,988). Pooling limited to trials of women at elevated risk reduced the estimated risk associated with aspirin use, but reduced statistical power (RR,* 1.09 [95% CI, 0.67 to 1.77]; n=12,366). Given a larger abruption risk with aspirin use in women at low risk (RR, 1.52 [95% CI, 0.68 to 3.29]), caution is warranted.

Table 6. Summary of Evidence for Benefits and Harms of Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia

Key Question(s)	# of Studies (k)	Design	Major Limitations	Consistency	Applicability	Overall Evidence	Summary of Findings
			the placebo group was unusually low; the event rate in the aspirin arm came closer to the general population risk of abruption. The multisite trial was U.S.-based, with a majority of participants identifying as racial or ethnic minorities (82%).				
	Postpartum hemorrhage (≥500 mL blood loss) *Elevated preeclampsia risk* k=6 n=12,860 *Low preeclampsia risk* k=3 n=9,900 Total n=22,760	RCT	The dosage of aspirin and the timing of use during pregnancy varied across studies. The MFMU trial instructed women to stop taking their medication if preeclampsia developed, whereas most protocols specified continued use until delivery. 5 studies stated specific endpoints (e.g., 10 days before the estimated date of delivery, 34 completed gestational weeks).	Only 6/15 studies in women at elevated risk reported this outcome and 4/6 could be pooled (2 had no events). 3/5 studies in low-risk women reported this outcome and all were pooled. Very low heterogeneity (I^2=0%; p=0.72). Consistent effects across multiple large studies. All studies of women at elevated risk close to null or toward reduced risk, all studies of women not at elevated risk close to null or toward harm.	Good applicability. Evidence on the outcome are from RCTs of women at elevated risk of preeclampsia taking low-dose aspirin, and women not at elevated risk taking low-dose aspirin. Most studies were conducted outside the U.S., but applicable to U.S. prenatal and hospital health care settings.	9 good Overall: Fair	Evidence showed no increased risk of postpartum hemorrhage (pooled RR,* 1.02 [95% CI, 0.96 to 1.09]; n=22,616) or increased blood loss for pregnant women taking low-dose aspirin. Results were consistent for women at elevated risk.
	Maternal blood loss *Elevated preeclampsia risk* k=4 n=416 *Low preeclampsia risk* k=2 n=2,332 Total n=2,748	RCT	Few studies representing a small subset of available data reported this outcome, only 1 good-quality trial included the outcome.	All studies found either a slightly lower mean blood loss or equivalent amounts of blood loss between study groups.	Good applicability.	1 good, 5 fair Overall: Fair to insufficient	We did not find evidence of maternal bleeding problems associated with low-dose aspirin use during pregnancy; however findings are not robust due to limited reporting. Meta-analysis was not conducted because there were few studies.

Table 6. Summary of Evidence for Benefits and Harms of Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia

Key Question(s)	# of Studies (k)	Design	Major Limitations	Consistency	Applicability	Overall Evidence	Summary of Findings
	Intracranial, intraventricular fetal bleeding *Elevated preeclampsia risk* k=6 n=12,433 *Low preeclampsia risk* k=4 n=10,024 Total n=22,457	RCT	Very rare event, insufficient power to detect even small effects. Different outcomes were reported across studies, some specifically reported intraventricular hemorrhage diagnosed on MRI and others reported any fetal bleeding problem.	Low heterogeneity (I^2=13.8%; p=0.33). Although few of the studies reporting this outcome observed any events, the rates in studies that did were nearly equal. Only 1 study found more cases in the aspirin group than the placebo group.	Good applicability. Evidence on the outcome are from RCTs of women at elevated risk of preeclampsia taking low-dose aspirin, and women not at elevated risk taking low-dose aspirin. Most studies were conducted outside the U.S., but would likely be similar to U.S. prenatal and hospital health care settings.	8 good, 2 fair Overall: Fair	We did not find evidence that aspirin use during pregnancy increased the risk of fetal or neonatal bleeding problems, such as intraventricular hemorrhage (pooled RR,* 0.87 [95% CI, 0.58 to 1.28]; n=22,158). The largest RCT (CLASP) observed 33 cases of intraventricular hemorrhage in the aspirin group and 45 (0.7%) in the control group (0.9%).
	Birth defects k=1 n=47,400	Perinatal cohort study	Details of the dose and frequency of aspirin use are unknown. Only 1 study meeting inclusion and risk of bias criteria was identified, and looks at only 1 type of birth defect in male offspring.	Only 1 study identified.	Some women in the study likely took higher single doses of aspirin, earlier in pregnancy, and with less regularity than would be the practice for prophylactic use of low-dose aspirin.	1 good Overall: Insufficient	Aspirin use during pregnancy was not associated with cryptorchidism in male neonates.
	Neurological and early child development outcomes k=1 n=4,365	RCT	Only 1 study meeting inclusion and risk of bias criteria was identified; other RCTs did not publish long-term followup data.	Only 1 study identified.	Data were from an RCT of women at risk of preeclampsia taking low-dose aspirin (60 mg); the findings are highly applicable.	1 good Overall: Insufficient	There were no differences in motor development or growth at 18 months by exposure to aspirin vs. placebo.

* Some studies were excluded from this pooled analysis due to no events.

† Four studies did not report standard deviations for birth weights and were therefore excluded from this pooled analysis.

Abbreviations: CI = confidence Interval; CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; HELLP = hemolysis, elevated liver enzymes, low platelet count; IUGR = intrauterine growth restriction; KQ = key question; RCT = randomized, controlled trial; RR = relative risk; SGA = small for gestational age.

Table 7. Number Needed to Treat for Three Levels of Risk for Preeclampsia, IUGR, and Preterm Birth

Outcome	Risk of outcome	RR	Absolute change in risk	Risk after change	NNT Benefit (95% CI)	NNT Harm (95% CI)
Preeclampsia	0.10	0.76	-0.02	0.08	42 (26, 200)	NA
	0.18	0.76	-0.04	0.14	23 (15, 111)	NA
	0.23	0.76	-0.06	0.17	18 (11, 87)	NA
IUGR	0.07	0.80	-0.01	0.06	71 (41, 1429)	NA
	0.13	0.80	-0.03	0.10	38 (22, 769)	NA
	0.24	0.80	-0.05	0.19	21 (12, 417)	NA
Preterm birth	0.11	0.86	-0.02	0.09	65 (38, 455)	NA
	0.19	0.86	-0.03	0.16	38 (22, 263)	NA
	0.31	0.86	-0.04	0.27	23 (13, 161)	NA
Abruption (in women at increased risk)	0.015	1.12	0.002	0.017	NA	556 (145 harm to ∞ to 476 benefit)
	0.020	1.12	0.002	0.022	NA	417 (109 harm to ∞ to 357 benefit)
Abruption (across all risk levels)	0.015	1.17	0.0026	0.018	NA	392 (139 harm to ∞ to 952 benefit)
	0.020	1.17	0.0034	0.023	NA	294 (104 harm to ∞ to 714 benefit)

Abbreviations: IUGR = intrauterine growth restriction; NNT = number needed to treat; RR = relative risk.

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

Level of Risk	Risk Factors
High risk† *Single risk factors consistently associated with the greatest risk of preeclampsia*	Prior preeclampsia Multiple gestation pregnancy Chronic hypertension Type 1 or 2I diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)
Moderate risk‡ *The presence of multiple moderate risk factors may be used by clinicians to identify women at high risk of preeclampsia*	Never having borne children Obesity (i.e., BMI >30 kg/m^2) Family history of preeclampsia (i.e., mother, sister) Sociodemographic characteristics (i.e., black race, low socioeconomic status) Age ≥35 years Personal history factors (e.g., born low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)
Low risk	Prior uncomplicated term delivery

*Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasound, also may additionally be used by some clinicians to evaluate risk.
†Preeclampsia incidence rates would be expected to be 8% or greater in pregnant women with 1 or more of these risk factors.
‡These risk factors are independently associated with moderate preeclampsia risk, some more consistently than others.

Key Question Literature Search Strategies

Database: **Ovid MEDLINE**(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid MEDLINE(R) Daily Update <January 21, 2013>

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1 Pregnancy/ (658667)
2 pregnan$.ti,ab. (341659)
3 Pre-Eclampsia/ (21883)
4 Hypertension, Pregnancy-Induced/ (1258)
5 Eclampsia/ (3575)
6 preeclamp$.ti,ab. (11205)
7 eclamp$.ti,ab. (10638)
8 ((edema or proteinuria or hypertension) adj5 gestosis).ti,ab. (80)
9 eph gestosis.ti,ab. (433)
10 (tox?emi$ adj3 (eph or pregnan$)).ti,ab. (3016)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (732271)
12 Aspirin/ (36192)
13 Platelet Aggregation Inhibitors/ (24185)
14 aspirin.ti,ab. (34133)
15 acetylsalicylic acid.ti,ab. (6934)
16 antiplatelet$.ti,ab. (14123)
17 anti platelet.ti,ab. (2694)
18 (platelet adj3 (inhibitor$ or antiaggregant$ or antagonist$)).ti,ab. (5766)
19 12 or 13 or 14 or 15 or 16 or 17 or 18 (77920)
20 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. (648797)
21 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ (245203)
22 Meta-Analysis as Topic/ (12362)
23 clinical trial$.ti,ab. (187084)
24 controlled trial$.ti,ab. (97536)
25 random$.ti,ab. (623402)
26 20 or 21 or 22 or 23 or 24 or 25 (1212442)
27 11 and 19 and 26 (637)
28 Pregnancy/ (658667)
29 pregnan$.ti,ab. (341659)
30 28 or 29 (730270)
31 adverse effects.fs. (1261233)
32 harm$.ti,ab. (86890)
33 adverse.ti,ab. (246918)
34 Hemorrhage/ (48479)
35 h?emorrhag$.ti,ab. (169627)
36 bleed$.ti,ab. (127314)
37 blood loss.ti,ab. (28329)
38 31 or 32 or 33 or 34 or 35 or 36 or 37 (1735339)
39 Pregnancy complications/ (68804)

40 Maternal death/ (6)
41 Maternal mortality/ (7271)
42 Fetal death/ (22304)
43 Fetal mortality/ (213)
44 Congenital abnormalities/ (28816)
45 Postpartum hemorrhage/ (4314)
46 Abruptio Placentae/ (1704)
47 Abortion, Spontaneous/ (13505)
48 ((pregnan$ or maternal or f?etal or f?etus or neonat$) adj3 complication$).ti,ab. (12761)
49 ((congenital or birth or f?etal or f?etus) adj3 (defect$ or abnormal$ or anomal$)).ti,ab. (45623)
50 ((maternal or f?etal or f?etus) adj3 death$).ti,ab. (11168)
51 miscarr$.ti,ab. (7884)
52 spontaneous abortion$.ti,ab. (7888)
53 (placenta$ adj abruption$).ti,ab. (1207)
54 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 (189547)
55 30 and 38 (101741)
56 54 or 55 (261683)
57 19 and 56 (1649)
58 27 or 57 (1904)
59 limit 58 to english language (1558)
60 limit 59 to yr="2006 - 2013" (444)

Database: **Cochrane Database of Systematic Reviews, CENTRAL**

#1 pregnan*:ti,ab,kw or preeclamp*:ti,ab,kw or eclamp*:ti,ab,kw from 2006 to 2013, in Trials 4981
#2 aspirin:ti,ab,kw or "acetylsalicylic acid ":ti,ab,kw or antiplatelet*:ti,ab,kw or anti next platelet*:ti,ab,kw from 2006 to 2013, in Trials 1690
#3 platelet*:ti,ab,kw from 2006 to 2013, in Trials 2408
#4 inhibitor*:ti,ab,kw or antiaggregant*:ti,ab,kw or antagonist*:ti,ab,kw from 2006 to 2013, in Trials 15029
#5 #3 and #4 from 2006 to 2013, in Trials 1243
#6 #2 or #5 from 2006 to 2013, in Trials 2235
#7 #1 and #6 from 2006 to 2013, in Trials 49

Database: **PubMed, publisher-supplied**

Search	Query	Items found
#7	Search **(#6) AND English[Language]** Filters: **Publication date from 2006/01/01 to 2013/12/31**	4
#6	Search **#5 AND publisher[sb]**	10
#5	Search **#3 AND #4**	364
#4	Search **random*[tiab] OR clinical trial*[tiab] OR controlled trial*[tiab]**	782669
#3	Search **#1 AND #2**	1764

Search	Query	Items found
#2	Search **aspirin[tiab] OR antiplatelet*[tiab] OR anti platelet*[tiab] OR acetylsalicylic acid[tiab]**	52413
#1	Search **pregnan*[tiab] OR preeclamp*[tiab] OR eclamp*[tiab]**	355509

Systematic Evidence Review Search

Database: **AHRQ**

Aspirin Prophylaxis in Pregnancy [Chapter in Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force. 2nd edition US Preventive Services Task Force.] 1996 **ARCHIVED**

http://www.ncbi.nlm.nih.gov/books/NBK15451/

Database: **BMJ Clinical Evidence**

Pre-eclampsia, eclampsia, and hypertension, February 2011 (based on 2010 search)
http://clinicalevidence.bmj.com/x/pdf/clinical-evidence/en-gb/systematic-review/1402.pdf

Database: **Cochrane Database of Systematic Reviews** (Issue 12 of 12, Dec 2012)

#1 "preeclampsia":ti,ab,kw
#2 "pre eclampsia":ti,ab,kw
#3 "preeclamptic":ti,ab,kw
#4 "pre eclamptic":ti,ab,kw
#5 "hypertension":ti,ab,kw
#6 "hypertensive":ti,ab,kw
#7 #5 or #6
#8 "pregnancy":ti,ab,kw
#9 "pregnant":ti,ab,kw
#10 #8 or #9
#11 #7 and #10
#12 #1 or #2 or #3 or #4 or #11
#13 "aspirin":ti,ab,kw
#14 "antiplatelet":ti,ab,kw
#15 "anti platelet":ti,ab,kw
#16 "antiplatelets":ti,ab,kw
#17 "anti platelets":ti,ab,kw
#18 #13 or #14 or #15 or #16 or #17
#19 #12 and #18 (limit to 2007-2012)

Database: **DARE**

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1 (preeclampsia) OR (preeclamptic) OR (pre eclampsia) OR (pre eclamptic)

2 (hypertension) OR (hypertensive)
3 (pregnant) OR (pregnancy)
4 #2 AND #3
5 #1 OR #4
6 (aspirin) OR (antiplatelet) OR (anti platelet) OR (antiplatelets) OR (anti platelets)
7 #5 AND #6 FROM 2007 TO 2012

Database: **NICE**

Hypertension in pregnancy: NICE guideline. October 2012
http://www.nice.org.uk/nicemedia/live/13098/50418/50418.pdf

Database: **Pubmed**
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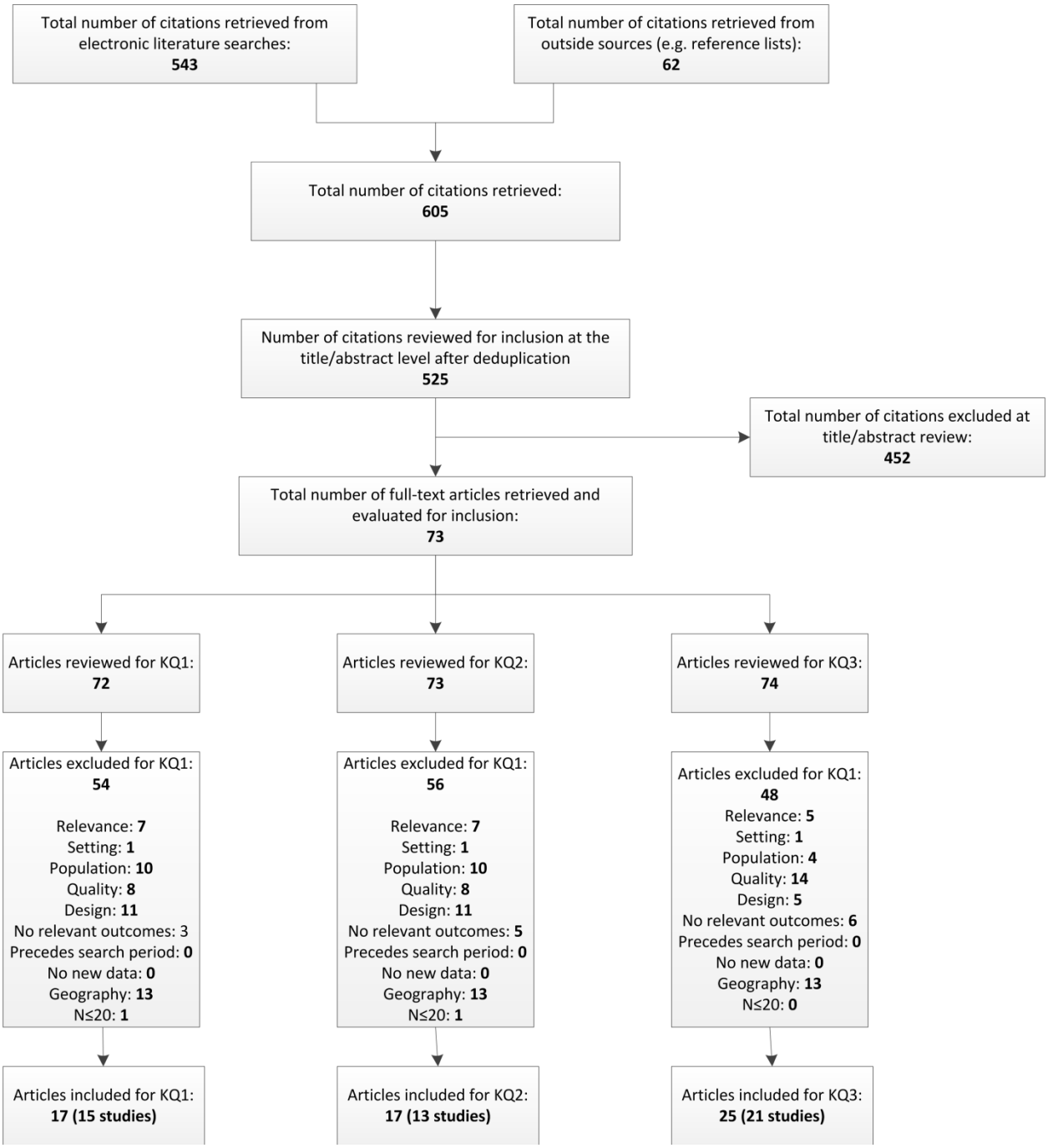
1) ("Hypertension, Pregnancy-Induced"[Mesh:NoExp] OR "Eclampsia"[Mesh:NoExp] OR "Pre-Eclampsia"[Mesh:NoExp])
2) ("Aspirin"[Mesh:noexp] OR "Platelet Aggregation Inhibitors" [Mesh:noexp] OR "Platelet Aggregation Inhibitors" [Pharmacological Action])
3) #1 AND #2
4) #3 AND systematic[sb]
5) (pre eclampsia[Title/Abstract] OR preeclampsia[Title/Abstract] OR pre eclamptic[Title/Abstract] OR preeclamptic[Title/Abstract])
6) (aspirin[Title/Abstract] OR antiplatelet[Title/Abstract] OR anti platelet[Title/Abstract] OR antiplatelets[Title/Abstract] OR anti platelets[Title/Abstract])
7) #5 AND #6
8) #7 AND systematic[sb]
9) #3 OR #8
10) limit to English[Language] AND ("2007"[Date - Publication] : "3000"[Date - Publication])

Appendix A Figure 1. Literature Flow Diagram



Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Populations	Efficacy (KQs 1, 2): *Pregnant women at elevated risk for preeclampsia based on:* Patient characteristics, medical history, diagnostic measurements or assays (e.g., uterine artery Doppler, biomarkers) Chemoprevention harms (KQ 3): Pregnant women, fetuses, infants	Nonhuman populations; males; nonpregnant women; studies that only/exclusively include individuals seeking fertility treatment; other selected nongeneralizable populations
Disease/ condition	Primary prevention of preeclampsia	Secondary and tertiary prevention of preeclampsia
Setting	Developed countries, as defined by the Human Development Index in "very high human development" category.	Countries not categorized as "very high human development," concern for nutritional deficiencies in developing countries
Interventions	Aspirin (50 to 150 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, weight loss)
Outcomes	***Maternal:*** ▪ Organ/system injury or failure: - HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) - Eclampsia, puerperal cerebrovascular disorder, cerebrovascular hemorrhage, edema, or embolus - Renal or hepatic injury/failure - Pulmonary edema, Adult Respiratory Distress Syndrome - Disseminated Intravascular Coagulation ▪ Failed induction of labor ▪ Caesarean delivery (medically indicated or due to failed induction of labor and/or complications of labor) ▪ Abruptio placentae ▪ Mental health ▪ Maternal mortality ***Fetal:*** ▪ Preterm birth (<37 weeks), very preterm birth (<32 weeks), extremely preterm birth (<28 weeks); mean gestational age ▪ Low birth weight (≤2500 g), very low birth weight (≤1500 g), extremely low birth weight (≤1000 g) ▪ Intrauterine growth restriction/small for gestational age (<10th percentile weight for gestational age) ▪ Complications from Caesarean delivery, labor induction, or eclampsia prophylaxis (e.g., low Apgar score, ventilation needed) ▪ Perinatal/neonatal mortality ***Harms from treatment:*** ▪ Abruptio placentae, intracranial fetal bleeding, postpartum hemorrhage, fetal malformations, behavioral or developmental problems	▪ Intermediate outcomes, such as length of hospital stay (without indication) ▪ Intensive care unit admission ▪ Neonatal intensive care unit admission
Study Designs	Efficacy (KQs 1, 2): RCT only Chemoprevention harms (KQ 3): RCT or observational study (case series, cohort, registry) data	Efficacy (KQs 1, 2): Any design other than RCT Harms (KQ 3): Editorial, narrative review, commentary, postmarketing surveillance, case reports
Study Quality	Good and fair quality	Poor quality
Language	English	Non-English studies

Appendix A Table 2. Quality Assessment Criteria

Design	U.S. Preventive Services Task Force Quality Rating Criteria[48]	National Institute for Health and Clinical Excellence Methodology Checklists[51]
Systematic reviews and meta-analyses	• Comprehensiveness of sources considered/search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance are especially important for systematic reviews	• Study addresses an appropriate and clearly focused question • Description of the methodology used is included • Literature search is sufficiently rigorous to identify all the relevant studies • Study quality is assessed and taken into account • There are enough similarities between the studies selected to make combining them reasonable
Case-control studies	• Accurate ascertainment of cases • Nonbiased selection of cases/controls with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Measurement of exposure accurate and applied equally to each group • Appropriate attention to potential confounding variables	• Study addresses an appropriate and clearly focused question • Cases and controls are taken from comparable populations • Same exclusion criteria are used for both cases and controls • Percentage of each group (cases and controls) that participated in the study is reported • Comparison is made between participants and nonparticipants to establish their similarities or differences • Cases are clearly defined and differentiated from controls • It is clearly established that controls are noncases • Measures have been taken to prevent knowledge of primary exposure influencing case ascertainment • Exposure status is measured in a standard, valid, and reliable way • Main potential confounders are identified and taken into account in the design and analysis • Confidence intervals are provided
Randomized, controlled trials	• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements are equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes are considered	• Study addresses an appropriate and clearly focused question • Assignment of subjects to treatment groups is randomized • Adequate concealment method is used • Subjects and investigators are kept “blind” about treatment allocation • Treatment and control groups are similar at the start of the trial • Only difference between groups is the treatment under investigation • All relevant outcomes are measured in a standard, valid, and reliable way • Percentage of the individuals or clusters recruited into each treatment arm of the study that dropped out before the study was completed is reported • All subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis) • When the study is carried out at more than one site, results are comparable for all sites

Appendix A Table 2. Quality Assessment Criteria

Design	U.S. Preventive Services Task Force Quality Rating Criteria[48]	National Institute for Health and Clinical Excellence Methodology Checklists[51]
Cohort studies	• Initial assembly of comparable groups employs consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to followup or overall high loss to followup • Measurements are equal, reliable, and valid (includes masking of outcome assessment) • Clear definition of the interventions • All important outcomes are considered	• Study addresses an appropriate and clearly focused question • Two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation • Study indicates how many of the people asked to take part did so, in each of the groups being studied • Likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis • Percentage of individuals or clusters recruited into each arm of the study that dropped out before the study was completed is reported • Comparison is made between full participants and those lost to followup, by exposure status • Outcomes are clearly defined • Assessment of outcome is made blind to exposure status • When blinding is not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome • Measure of assessment of exposure is reliable • Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Exposure level or prognostic factor is assessed more than once • Main potential confounders are identified and taken into account in the design and analysis • Confidence intervals are provided

Appendix B. Ongoing or Recently Completed Studies

Study, Year initiated	Design	Aim	Location	Number of participants	Intervention description	Relevant outcomes	2013 status
Odibo, 2012	RCT	Determine the efficacy of low-dose aspirin for preventing preeclampsia in women identified as high risk by a first trimester multiparameter predictive model	United States	Estimated enrollment: 220	Aspirin (81 mg per day) until 37 weeks of gestation or labor, whichever comes first	Preeclampsia	Estimated completion: September 2014
Nicolaides, 2011	RCT	To examine if the prophylactic use of low-dose aspirin from the first-trimester of pregnancy in women at increased risk for preeclampsia can reduce the incidence and severity of the disease	United Kingdom	Estimated enrollment: 1,560	Aspirin (75 mg per day) from 12 to 34 weeks of gestation or labor, whichever comes first	Preeclampsia, harms	Estimated completion: September 2016
Perrotin, 2012	RCT	Determine the efficacy of low-dose aspirin, given at bedtime and started early during pregnancy, in nulliparous pregnant women selected as high-risk by the presence of a bilateral uterine artery notch or bilateral uterine artery PI ≥1.7 during the first trimester ultrasound scan, to prevent the occurrence of preeclampsia	France	Estimated enrollment: 4,972	Aspirin (160 mg per day) until 34 weeks of gestation	Preeclampsia	Estimated completion: June 2015
Varea, 2012	RCT	Determine whether low-dose aspirin improves trophoblastic invasion evaluated at third trimester in women defined as high-risk by abnormal uterine artery Doppler at first trimester	Spain	Estimated enrollment: 270	Aspirin (150 mg per day)	Uterine artery mean pulsatility; preeclampsia	Estimated completion: December 2013

Appendix C. Excluded Studies*

**This is a listing of studies excluded from the review by KQ. If a study was included for one KQ, but excluded for others, it would still be listed here with the excluded KQs noted.*

Exclusion Code
E1. Study relevance
E2. Setting
E3. Population **E3a:** Nulliparous otherwise healthy women
E4: Study quality
E5: Study design
E6: No relevant outcomes
E7: Precedes search period
E8: Provides no new data not otherwise covered in other articles for this study
E9: Geography

1. Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. Italian Study of Aspirin in Pregnancy. Lancet 1993 Feb 13;341(8842):396. PMID: 8094168. KQ1E4, KQ2E4, KQ3E4.

2. Bakhti A, Vaiman D. Prevention of gravidic endothelial hypertension by aspirin treatment administered from the 8th week of gestation.[Erratum appears in Hypertens Res. 2012 Feb;35(2):244]. Hypertension Research - Clinical & Experimental 2011 Oct;34(10):1116-20. PMID: 21881579. KQ1E9, KQ2E9, KQ3E9.

3. Benigni A, Gregorini G, Frusca T, et al. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. N Engl J Med 1989 Aug 10;321(6):357-62. PMID: 2664523. KQ2E6.

4. Byaruhanga RN, Chipato T, Rusakaniko S. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. International Journal of Gynecology & Obstetrics 1998 Feb 1;60(2):129-35. PMID: 9509950. KQ1E9, KQ2E9, KQ3E9.

5. Chandiramani M, Seed P, Poston L, et al. Antiplatelet agents for prevention of pre-eclampsia. Lancet 2007 Nov 17;370(9600):1685-6. PMID: 18022031. KQ1E5, KQ2E5, KQ3E5.

6. Chiaffarino F, Parazzini F, Paladini D, et al. A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia. European Journal of Obstetrics & Gynecology and Reproductive Biology 2004 Feb 10;112(2):142-4. PMID: 14746947. KQ1E4, KQ2E4, KQ3E4.

7. Cowchock S, Reece EA. Do low-risk pregnant women with antiphospholipid antibodies need to be treated? Organizing Group of the Antiphospholipid Antibody Treatment Trial. Am J Obstet Gynecol 1997 May;176(5):1099-100. PMID: 9166175. KQ1E3, KQ2E3, KQ3E6.

8. Cruickshank DJ, Robertson AA, Campbell DM, et al. Maternal Obstetric Outcome Measures in A Randomised Controlled Study of Labetalol in the Treatment of Hypertension in Pregnancy. Hypertension in Pregnancy 1991 Jan 1;b10(3):333-44. PMID: none. KQ1E1a, KQ2E1a, KQ3E1a.

9. Dasari R, Narang A, Vasishta K, et al. Effect of maternal low dose aspirin on neonatal platelet function. Indian Pediatr 1998 Jun;35(6):507-11. PMID: 10216644. KQ1E9, KQ2E9, KQ3E9.

10. Davies NJ, Gazvani MR, Farquharson RG, et al. Low-Dose Aspirin in the Prevention of Hypertensive Disorders of Pregnancy in Relatively Low-Risk Nulliparous Women. Hypertension in Pregnancy 1995;14(1):49-55. PMID: none. KQ1E3a, KQ2E3a

11. Ebrashy A, Ibrahim M, Marzook A, et al. Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery Doppler ultrasound at 14-16 weeks pregnancy: randomized controlled clinical trial. Croat Med J 2005 Oct;46(5):826-31. PMID: 16158479. KQ1E9, KQ2E9, KQ3E9.

12. Elder MG, de SM, Sullivan M. A randomised trial of low dose aspirin for primiparae in pregnancy (Golding)/Barbados low dose aspirin study in pregnancy (BLASP) (Rotchell et al.). Br J Obstet Gynaecol 1999

Feb;106(2):180. PMID: 10426687. KQ1E5, KQ2E5, KQ3E5.
13. Gallery EDM, Ross MR, Hawkins M, et al. Low-Dose Aspirin in High-Risk Pregnancy? Hypertension in Pregnancy 1997 Jan 1;16(2):229-38. PMID: none. KQ2E6.
14. Goffinet F, Breart G, Uzan S. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. Br J Obstet Gynaecol 1996 Jul;103(7):719-20. PMID: 8688404. KQ1E9, KQ2E9, KQ3E9.
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16. Gunawardana L, Zammit S, Lewis G, et al. Examining the association between maternal analgesic use during pregnancy and risk of psychotic symptoms during adolescence. Schizophrenia Research 2011 Mar;126(1-3):220-5. PMID: 21146371. KQ1E1, KQ2E1, KQ3E4.
17. Hauth JC, Goldenberg RL, Parker CR, Jr., et al. Low-dose aspirin therapy to prevent preeclampsia. Am J Obstet Gynecol 1993 Apr;168(4):1083-91. PMID: 8475955. KQ1E3a, KQ2E3a.
18. Hermida RC, Ayala DE, Iglesias M, et al. Time-dependent effects of low-dose aspirin administration on blood pressure in pregnant women. Hypertension 1997 Sep;30(3 Pt 2):589-95. PMID: 9322987. KQ3E6.
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20. Hermida RC, Ayala DE, Iglesias M. Administration time-dependent influence of aspirin on blood pressure in pregnant women. Hypertension 2003 Mar;41(3 Pt 2):651-6. PMID: 12623974. KQ1E6, KQ2E6, KQ3E6.
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25. Kincaid-Smith P, North RA, Fairley KF, et al. Prevention of pre-eclampsia in high risk women with renal disease: A prospective randomized trial of heparin and dipyridamole. Nephrology 1995 Aug 1;1(4):297-300. PMID: none. KQ1E1a, KQ2E1a, KQ3E1a.
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Nov;35(4):370-4. PMID: 8717556. KQ1E3, KQ2E3.
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Appendix D Table 1. Methodological and Intervention Characteristics of Included Studies

Study, Year Study quality	Study design	Country	N randomized or included	Preeclampsia risk criteria	Dose Time of initiation and stopping treatment	Preeclampsia incidence reported
Ayala, 2012[59] Good	RCT	Spain	350	Receiving medical care at a high-risk unit. High risk includes: family or personal history of PE; chronic HTN; CVD; endocrine, metabolic, or bleeding disease; history of spontaneous abortion; multiple pregnancy; obesity; or age.	100 mg daily 12 to 16 weeks; delivery	Yes
Benigni,1989[60] Fair	RCT	Italy	33	HTN or previous obstetrical history (fetal death due to placental insufficiency, severe IUGR, early-onset PE [<32 weeks])	60 mg daily 12 weeks; delivery	No
Caspi, 1994[61] Good	RCT	Israel	47	Twin pregnancies	100 mg daily 15 to 23 weeks (mean, 17.7 weeks); delivery	Yes
CLASP, 1994[58] Good	RCT	Argentina, Australia, Belgium, Canada, Germany, Hong Kong, Israel, Malaysia, New Zealand, Russia, Spain, Sweden, Netherlands, United Arab Emirates, UK, USA	9,364	Population at risk of PE or IUGR as determined by a clinician (women were considered for prophylactic entry or therapeutic entry) *Prophylactic entry:* Pregnant women with history of PE or IUGR in a previous pregnancy, chronic HTN, renal disease, or other risk factors, such as maternal age, family history, or multiple pregnancy *Therapeutic entry:* Pregnant women with signs or symptoms of PE or IUGR in the current pregnancy	60 mg daily 12 to 32 weeks; delivery	Yes
Davies, 1995[76]† Fair	RCT	UK	122	Population not at elevated risk, healthy nulliparous women (study included for KQ3 only)	75 mg daily 18 weeks; delivery	Yes
Gallery, 1997[62] Fair	RCT	Australia	108	Preexisting chronic HTN, renal disease, or history of PE as determined by patient interview at 16 weeks' gestation	100 mg daily 17 to 19 weeks; 2 weeks prior to planned delivery	No
Grab, 2000[63] Fair	RCT	Germany	43	Current IUGR, impaired uteroplacental blood flow, chronic HTN, or prior history of PE, stillbirth, or growth restriction	100 mg daily 18 weeks; 38 weeks	Yes
Hauth, 1993[73]† Good	RCT	US	606	Population not at elevated risk, healthy nulliparous women (study included for KQ3 only)	60 mg daily 23 weeks; delivery	Yes
Hermida, 1997[64] Good	RCT	Spain	100	Being treated at the HR unit of the hospital (reasons include family or personal history of gestational HTN, PE, or chronic HTN; cardiovascular, endocrine, bleeding, or metabolic disease; and a personal history of spontaneous abortion, multiple pregnancy, obesity; adolescent or middle-aged nulliparous pregnancy [<18 or >35 years])	100 mg daily 12 to 16 weeks; delivery	Yes

Appendix D Table 1. Methodological and Intervention Characteristics of Included Studies

Study, Year Study quality	Study design	Country	N randomized or included	Preeclampsia risk criteria	Dose Time of initiation and stopping treatment	Preeclampsia incidence reported
Jensen, 2010[77]† Good	Cohort	Denmark	47,400	Population not at elevated risk, all children born to women who were pregnant between 1996 and 2002 were enrolled (study included for KQ3 only)	NR Anytime throughout pregnancy	No
Keim, 2006[78]† Good	Case-control	US	3,129	Early fetal loss in a previous pregnancy (study included for KQ3 only)	NR Anytime throughout pregnancy	No
McParland, 1990[65] Fair	RCT	UK	106	Persistent abnormal Doppler flow-velocity waveforms at 24 weeks' gestation (measured twice)	75 mg daily 24 weeks; delivery	Yes
MFMU, 1998[57] Good	RCT	US	2,539	Medical history that places women in 1 of 4 high-risk groups: women with DM, women with chronic HTN, women with multifetal gestations, women with previous PE. Women with DM could also have HTN (but analyzed with DM group), but women with multifetal gestations were excluded if they also had DM or HTN.	60 mg daily 13 to 26 weeks; delivery or if PE develops	Yes
Newnham, 1995[79]† Good	RCT	Australia	51	Population not at risk for PE, population at risk for IUGR (study included for KQ3 only)	100 mg 28 to 36 weeks; delivery	No
Rotchell, 1998[75]† Good	RCT	Barbados	3,647	Population not at elevated risk, healthy women without contraindication for aspirin therapy (study included for KQ3 only)	75 mg daily 12 to 32 weeks; delivery	Yes
Schiff, 1989[66] Good	RCT	Israel	65	At least 1 of the following: nulliparity, twin gestation, history of PE, and positive rollover test result	100 mg daily 28 or 29 weeks; 38 weeks	Yes
Sibai, 1993[72]† Good	RCT	US	3,135	Population not at elevated risk, healthy nulliparous women (study included for KQ3 only)	60 mg daily 13 to 25 weeks; delivery	Yes
Subtil, 2003[74]† Good	RCT	France and Belgium	3,294	Population not at elevated risk, healthy nulliparous women (study included for KQ3 only)	100 mg daily 14 to 20 weeks; 34 weeks	Yes
Vainio, 2002[67] Fair	RCT	Finland	90	Bilateral diastolic notch identified by transvaginal Doppler ultrasound and risk of PE or IUGR as determined by medical history	0.5 mg/kg daily 12 to 14 weeks; not clearly specified	Yes
Viinikka, 1993[68] Fair	RCT	Finland	208	Diagnosis of arterial HTN (BP without treatment >140/90 mm Hg before pregnancy), or history of severe PE	50 mg daily 15 to 16 weeks; delivery	Yes
Villa, 2012[69] Fair	RCT	Finland	152	Age, BMI >30 kg/m^2, chronic HTN, Sjorgren's syndrome or lupus, a history of gestational diabetes, PE, small for gestational age, fetus mortus, and 2nd-degree diastolic notch present at 12+0 weeks through 13+6 weeks' gestation	100 mg daily Initiated at 12 to 13 weeks' gestation; stopping at 35 weeks or delivery	Yes

Appendix D Table 1. Methodological and Intervention Characteristics of Included Studies

Study, Year Study quality	Study design	Country	N randomized or included	Preeclampsia risk criteria	Dose Time of initiation and stopping treatment	Preeclampsia incidence reported
Wallenburg, 1986[70] Good	RCT	The Netherlands	46	Angiotensin-II sensitivity determined by blood test	60 mg daily 26 weeks; delivery	Yes
Yu, 2003[71] Good	RCT	Brazil, Chile, South Africa, UK	560	Women with a mean PI >1.6 and early diastolic notching of uterine arteries identified by transvaginal color Doppler ultrasound	150 mg daily 22 to 24 weeks; 35 weeks*	Yes

* Estimated.
† Study is included for analysis of KQ3 (harms only) and is not in a high-risk population.

Abbreviations: BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; IUGR = intrauterine growth restriction; NR = not reported; PE = preeclampsia; RCT = randomized; controlled trial.

Appendix D Table 2. Study Population Baseline Characteristics of Included Studies

Study, year Quality	Major inclusion criteria	Major exclusion criteria	Mean age, *y* (SD)	% White, nonHispanic	Mean BMI (kg/m^2)	Nulliparous, %	Health behaviors and conditions, %
Ayala, 2012[59] Good	Higher risk for gestational HTN or PE and receiving medical care and followup at the Obstetric Physiopathology Service (high-risk unit) of the hospital; gestational age ≤16 weeks at randomization and maternal age ≥18 years	Multiple pregnancy, chronic HTN, use of BP-lowering medication, CVD, chronic liver disease, use of anti-inflammatory medication, DM or other endocrine disease such as hyperthyroidism, history of drug/alcohol abuse, night/ shiftwork employment, AIDS, intolerance to ABPM	IG: 30.3 (5.3) CG: 31.1 (5.2)	NR	IG: 25.4 (4.3) CG: 25.5 (4.2)	IG: 49.4 CG: 55.1	*Previous abortion:* IG: 31.3 CG: 30.5
Benigni, 1989[60] Fair	At high risk for PE due to chronic HTN or previous obstetrical history (fetal death due to placental insufficiency, severe IUGR, early onset PE [<32 weeks])	Presence of antiphospholipid antibodies (lupus-like, anticoagulant, anticardiolipin)	IG: 31.0 (5) CG: 32.0 (6)	NR	NR	NR	*Chronic HTN:* IG: 35.2* CG: 31.3* *Smoking history:* IG: 5.9 CG: 0
Caspi, 1994[61] Good	All pregnant women with uncomplicated twin pregnancies at the start of their second trimester	Chronic renal, cardiovascular, pulmonary or hepatic disorders; past or present coagulopathy or peptic ulcer, gestational diabetes; known hypersensitivity to ASA	IG: 28.8 (4.4) CG: 27.8 (4.5)	NR	NR	IG: 41.7* CG: 30.4*	
CLASP, 1994[58]‡ Good	Pregnant women between 12 and 32 weeks' gestation and, in the opinion of the clinician, at sufficient risk of PE or IUGR (women were considered for prophylactic entry or therapeutic entry)	Increased risk of bleeding, asthma, allergy to aspirin, high likelihood of immediate delivery	IG: 28.5 (5.4) CG: 28.5 (5.5)	NR	NR	IG: 28.0 CG: 28.0	*Current smoker:* IG: 21.0 CG: 20.0
Davies, 1995[76]# Fair	Pregnant women with no previous pregnancy proceeding past 12 weeks' gestation and hemoglobin concentration >13.2 g/dL between 12 and 19 weeks' gestation	Multiple pregnancy, DM, recurrent spontaneous abortions, or any contraindication to aspirin therapy	IG: 25.4 (5.5) CG: 25.4 (4.2)	IG: 96.6 CG: 95.0	*Mean weight (kg) (SD):* IG: 65.7 (16.4) CG: 72.0 (13.9)	IG: 100 CG: 100	*Current smoker:* IG: 10.3 CG: 13.3
Gallery, 1997[62] Fair	Pregnant women with preexisting chronic HTN, preexisting renal disease, or previous PE	Pregnant women with a history of aspirin allergy, aspirin-sensitive asthma, preexisting bleeding diathesis, or having a multiple pregnancy	IG: 29 (23 to 28)§ CG: 28 (22 to 38)§	IG: 96.0 CG: 95.0	NR	IG: 42.0 CG: 43.0	NR

Appendix D Table 2. Study Population Baseline Characteristics of Included Studies

Study, year Quality	Major inclusion criteria	Major exclusion criteria	Mean age, *y* (SD)	% White, nonHispanic	Mean BMI (kg/m^2)	Nulliparous, %	Health behaviors and conditions, %
Grab, 2000[63] Fair	Singleton pregnancies of <20 weeks' gestation with early IUGR, impaired uteroplacental blood flow, chronic HTN or history of stillbirth, growth restriction or PE	Patients with diabetes mellitus, pre-existing proteinuric HTN or fetal malformations or chromosome abnormalities	NR	NR	NR	NR	NR
Hauth, 1993[73]# Good	Nulliparous, age ≤28 years and ≤22 weeks of gestation	History of illness or conditions known to increase the incidence of PE or PIH (i.e., renal disease, collagen vascular disease, DM, multifetal gestation, chronic HTN)	IG: 20.3 (2.6) CG: 20.4 (2.7)	IG: 30.0 CG: 27.0	NR	100	NR
Hermida, 1997[64] Good	Being treated at the HR unit of the hospital, absence of any condition requiring the use of antihypertensive medications, maternal age 18–40 years, and gestational age <16 weeks	Multiple pregnancy, chronic HTN, chronic liver disease, any disease requiring the use of anti-inflammatory medications, DM or any other endocrine disease, intolerance to the use of an ambulatory BP monitor	IG: 30.3 (0.9) CG: 30.1 (0.8)	NR	NR	*Primiparous:* All: 70%	NR
Jensen, 2010[77]# Good	All children born to women who were pregnant between 1996 and 2002 and intended to carry their pregnancy to term	Those that did not end with at least 1 live birth, those with female offspring, those with twin or higher multiple births, and pregnancies in which boys or mothers were not uniquely identifiable	All children were age 18 months at followup	NR	NR	*Primiparous:* Un: 48.2 Ex: 44.5	*DM:* Un: 1.3 Ex: 1.3
Keim, 2006[78]# Good	All cases experienced early fetal loss in a previous pregnancy	NR	Cases: 26.9 (6.5) Controls: 25.2 (5.7)	Cases: 62.0 Controls: 66.0	NR	NR	NR
McParland, 1990[65] Fair	All women attending St. Georges hospital for routine ultrasound with repeat abnormal Doppler waveforms at 24 weeks	Known ASA allergy; maternal diabetes; bleeding disorders; peptic ulceration; systemic lupus erythematosus	IG: 25.6 (4.2) CG: 26.5 (5.1)	IG: 73.0 CG: 65.0	NR	IG: 79.2* CG: 75.0*	*Smoking during pregnancy:* IG: 23.0 CG: 16.0
MFMU, 1998[57]† Good	In 1 of 4 high-risk PE groups: pregestational insulin-treated DM, chronic HTN, multifetal gestations, and PE in a previous pregnancy	Multifetal gestations if subject also had DM, HTN, or proteinuria; history of PE and current proteinuria	DM: 26.0 (6) HTN: 30.0 (6) MG: 25.0 (6) PE: 25.0 (5)	DM: 53.0 HTN: 27.0 MG: 32.0 PE: 25.0	DM: 28.0 (7) HTN: 33.0 (9) MG: 27.0 (7) PE: 28.0 (8)	Total group: n=668	*Smoking during pregnancy:* DM: 22.0 HTN: 17.0 MG: 14.0 PE: 15.0

Appendix D Table 2. Study Population Baseline Characteristics of Included Studies

Study, year Quality	Major inclusion criteria	Major exclusion criteria	Mean age, *y* (SD)	% White, nonHispanic	Mean BMI (kg/m^2)	Nulliparous, %	Health behaviors and conditions, %
Newnham, 1995[79]# Good	Pregnant women with an ultrasound diagnosis of restricted fetal growth; gestational age between 28 and 36 weeks; no history of taking ASA during this pregnancy; no known contraindications to ASA use; expectation that the pregnancy would continue for at least another 14 days	NR	IG: 26.8 (7.2) CG: 28.6 (6.2)	NR	NR	IG: 48 CG: 65	*Smoking during pregnancy:* *<20 cigarettes/day:* IG: 40.0 CG: 35.0 *≥20 cigarettes/day:* IG: 8.0 CG: 0.0
Rotchell, 1998[75]# Good	Women between 12 and 32 weeks' gestation without contraindications such as: increased risk of bleeding, known allergy to aspirin, high likelihood of immediate delivery or previous placental abruption	NR	NR‖	NR	NR	*Primigravid:* IG: 44.0 CG: 44.0	*Previous pregnancy problems (multiparae):* IG: 8.0 CG: 7.0
Schiff, 1989[66] Good	Women with at least 1 of the following: nulliparity, twin gestation, history of PE; had to also screen positive during a roll-over test (which tested BP before and after rolling from the left side to back)	History of chronic HTN; long-term treatment with nonsteroidal antiinflammatory drugs or use of these drugs in prior 6 weeks; PIH detected before 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	IG: 27.1 (6.1) CG: 27.6 (5.7)	100	NR	NR	*Twin gestation:* IG: 8.8 CG: 6.5 *Gravidity, mean (SD):* IG: 1.58 (0.9) CG: 1.42 (0.7)
Sibai, 1993[72]# Good	Nulliparous; 13 to 25 weeks pregnant; BP <135/85 mm Hg; no proteinuria	History of chronic HTN, renal disease, diabetes, or other medical illnesses	IG: 20 (4.0) CG: 21 (5.0)	IG: 17.5 CG: 18.5	NR	100	*Multiple gestation:* IG: 1.3 CG: 1.2 *Smoking during pregnancy:* IG: 11.5 CG: 10.7

Appendix D Table 2. Study Population Baseline Characteristics of Included Studies

Study, year Quality	Major inclusion criteria	Major exclusion criteria	Mean age, *y* (SD)	% White, nonHispanic	Mean BMI (kg/m^2)	Nulliparous, %	Health behaviors and conditions, %
Subtil, 2003[74]# Good	Nulliparous, 14 to 20 weeks gestation, planned to continue prenatal care and give birth in the participating facility	History of HTN, potential indication (antiphospholipid antibodies or lupus) for aspirin, or a contraindication (allergy, hematomas or bleeding, hx of hemorrhage during surgery, tooth extraction or other, recent gastric or duodenal ulcer, severe asthma) to aspirin or other anticoagulant treatment during this pregnancy	IG: 24.7 (4.4) CG: 24.6 (4.4)	NR	IG: 22.5 (4.4) CG: 22.3 (4.2)	IG: 100 CG: 100	*Smoking history:* IG: 25.0 CG: 24.9
Vainio, 2002[67] Fair	Pregnant women at risk of PE or IUGR as determined by medical history and transvaginal Doppler ultrasound at 12 to 14 weeks' gestation	Gestational weeks <12 or >14, asthma, allergy to aspirin, previous peptic ulcer, or use of prostaglandin inhibitors within 10 days before investigation	IG: 30.6 (6.3) CG: 30.0 (5.9)	NR	*Weight (mean kg):* IG: 72.2 (2.5) CG: 72.4 (2.9)	IG: 34.9 CG: 23.3	*Previous IUGR:* IG: 14.0 CG: 23.3 *Previous pregnancy-induced HTN:* IG: 41.9 CG: 62.8 *Chronic HTN:* IG: 37.2 CG: 30.2
Viinikka, 1993[68] Fair	Women between 12 and 18 weeks of pregnancy with pre-existing arterial HTN or severe PE in previous pregnancy	NR	IG: 33.2 (4.9) CG: 32.7 (5.4)	NR	NR	IG: 25.2 CG: 23.8	*Pre-existing arterial HTN:* IG: 86.4 CG: 91.4
Villa, 2012[69] Fair	At least 1 of the following risk factors: age <20 or >40 years, BMI >30 kg/m^2, chronic HTN, Sjorgren's syndrome, lupus, history of gestational diabetes, history of preeclampsia, history of small for gestational age, or history of fetus mortus, and 2nd-degree diastolic notch present at 12+0 weeks' through 13+ 6 weeks' gestation	Allergy to aspirin, tobacco smoking during this pregnancy, multiple pregnancy. A history of 1 or more of the following: asthma, peptic ulcer, placental ablation, inflammatory bowel diseases, rheumatoid arthritis, haemophilia or thrombophilia	IG: 30.8 (5.3) CG: 31.0 (5.1)	NR	*Obesity (BMI >30 kg/m^2):* IG: 41 CG: 45	NR	*History of gestational diabetes:* IG: 6.6 CG: 16.7

Appendix D Table 2. Study Population Baseline Characteristics of Included Studies

Study, year Quality	Major inclusion criteria	Major exclusion criteria	Mean age, *y* (SD)	% White, nonHispanic	Mean BMI (kg/m^2)	Nulliparous, %	Health behaviors and conditions, %
Wallenburg, 1986[70] Good	Healthy primigravidae with an uncomplicated pregnancy of 26 weeks duration with sensitivity to angiotensin-II	NR	IG: 23.0 (17 to 38)¶ CG: 25.0 (19 to 36)¶	NR	NR	IG: 100 CG: 100	*Diastolic BP, mean (range):* IG: 75 (70 to 80) CG: 70 (60 to 80) *Smoking during pregnancy (10 to 20 per day):* IG: 21.7 CG: 17.4
Yu, 2003[71] Good	Women with singleton pregnancies and a mean uterine artery pulsatility index >1.6 at routine ultrasound between 22 and 24 weeks' gestation	Pre-existing HTN, renal disease or CVD, DM, bleeding disorders, systemic lupus erythematosus, peptic ulceration, hypersensitivity to aspirin, finding at 23-week scan of a fetal abnormality or fetal growth restriction	IG: 29 (23-33)¶ CG: 29 (24-33) ¶	IG: 66.3 CG: 58.3	IG: 25.0 CG: 25.6	IG: 26.8 CG: 23.4	*Mean uterine artery pulsatility index:* IG: 1.79 (1.70-1.98)‖ CG: 1.82 (1.71-1.98)‖ *Smoking history:* IG: 9.4 CG: 9.7

* Calculated.
† Baseline results only reported by the four high risk groups and not by IG/CG.
‡ Data presented here are for all study subjects, not only those entered for prophylaxis.
§ Mean (range).
‖ Mean age NR, authors report age, (%):

	IG	CG
<20:	24	24
20-29:	55	55
30-39:	20	20
>40:	1	1

¶ Median (IQR).
#Study is included for analysis of KQ3 (harms only) and is not in a high-risk population.

Abbreviations: ABPM = ambulatory blood pressure monitoring; ASA = acetylsalicylic acid; BMI = body mass index; BP = blood pressure; CG = control group; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; IG = intervention group; IUGR = intrauterine growth restriction; MG = multifetal gestation; NA = not applicable; NR = not reported; PE = preeclampsia; PIH = pregnancy-induced hypertension; SD = standard deviation.

We identified 15 trials that met inclusion criteria for the systematic review of potential preventive benefits of low-dose aspirin for women at elevated risk of preeclampsia, including two large trials (n>1000). An additional five randomized, controlled trials (RCTs) of low-dose aspirin to prevent preeclampsia in women at low preeclampsia risk[72-76] and two observational cohort studies[77,78] that measured aspirin exposure and outcomes during pregnancy were identified for inclusion in the evaluation of potential harms.

Studies for Evaluation of Benefits

A large, good-quality trial in the United States of 60 mg aspirin (MFMU 1998) was conducted in women at elevated risk of preeclampsia (n=2,503).[57] Women were recruited for participation at one of 13 study sites if they were 13 to 26 weeks pregnant and belonged to one of the following predefined preeclampsia risk categories: 1) pregestational diabetes mellitus, 2) chronic hypertension, 3) current multifetal gestation, and 4) preeclampsia in a prior pregnancy. Women with diabetes and hypertension were analyzed with the diabetes group, but women with multifetal pregnancies along with diabetes or hypertension were excluded. The risk criteria and recruitment sites generated a study population with a high preeclampsia incidence; in the control group, one in five women were diagnosed (20%). The majority of women recruited were racial and ethnic minorities; over half were black (56%), with smaller numbers of Hispanic and white participants. However, there was considerable variation in the distribution by risk group. Among the participants with diabetes, a majority were white (53%), whereas among women with previous preeclampsia, 71 percent were black, 4 percent Hispanic, and 25 percent white. Among study participants with multifetal gestations, 50 percent were black, 18 percent Hispanic, and 32 percent white, and among those with chronic hypertension, 61 percent were black, 12 percent Hispanic, and 27 percent white. The average BMI reported at baseline suggests that many participants were overweight, particularly in the chronic hypertension group (mean BMI, 33 [SD, 9]). In addition, reported smoking rates during pregnancy were high in women with diabetes (22%) and chronic hypertension (17%). Unlike the other included trials, the MFMU protocol instructed women to stop taking their medication if they developed preeclampsia, limiting the ability to observe any benefits that might accompany aspirin use in women once the condition develops.

The largest included study was a multinational trial of 60 mg aspirin managed by a U.K.-based collaborating center (n=9,364) (CLASP 1994).[58] The CLASP group included 16 diverse study sites (e.g., Malaysia, Spain, United Arab Emirates, Hong Kong, Canada, Germany, the United States, Sweden), but two thirds of the study participants were recruited in the United Kingdom, and some sites contributed as few as seven participants (United States). CLASP was designed as a pragmatic trial, wherein women at elevated risk of developing preeclampsia or having preeclampsia or IUGR were identified based on personal and/or medical history. Prior preeclampsia or IUGR, chronic hypertension, renal disease or other risk factors, such as age, family history, or multifetal pregnancy were identified risk factors for preeclampsia. The study authors indicated that the "fundamental criterion for entry was that the responsible clinician was uncertain whether or not to recommend aspirin in the individual pregnancy." Treatment could begin as early as 12 weeks' gestation and participants were instructed to continue until delivery. Nearly two thirds of study participants began treatment before 20 weeks' gestation.

CLASP participants were categorized according to whether they were enrolled in the study for prophylactic or therapeutic reasons. For the purpose of our review of the preventive benefits of aspirin for morbidity and mortality from preeclampsia, we include only the prophylactic participants in our pooled analyses where possible (maternal n=7,974; fetal n=8,257). The overall incidence of preeclampsia in the control arm of the prophylactic trial population was relatively low (8%).

An international trial by Yu et al (2003) of 150 mg aspirin was conducted at 10 sites: seven in the United Kingdom and one each in Brazil, Chile, and South Africa.[71] The study enrolled 560 women considered at elevated risk of preeclampsia based on results of a transvaginal color Doppler assessment of the uterine artery. Women undergoing routine ultrasonography at 22 to 24 weeks' gestation were offered a test of their mean pulsatility index. Those with readings greater than 1.6 were eligible to participate in the trial. Aspirin or an identical placebo were taken from the time of recruitment until 35 weeks' gestation. The protocol obtained a population of women with preeclampsia incidence of 19 percent.

Two good-quality trials conducted in Spain by the same research group and published 15 years apart met the review inclusion criteria.[59,64] Both trials tested 100 mg of aspirin started at 12 to16 weeks in women at elevated preeclampsia or gestational hypertension risk because they were receiving treatment at a hospital specializing in high-risk pregnancies. Reasons women could receive care at the unit included prior personal or family history of gestational or chronic hypertension or preeclampsia or cardiovascular, endocrine, bleeding, or metabolic disease, and a personal history of spontaneous abortion, multiple pregnancy, obesity, and adolescent or middle aged nulliparity, among other things. For both trials, women age 18 years and older and those with multifetal pregnancies, chronic hypertension, any condition requiring hypertension or antiplatelet medications, and other health conditions were excluded, as well as inability or unwillingness to comply with the trial protocols. The trial protocol was more demanding than for other preeclampsia trials we reviewed, because 24-hour blood pressure monitoring was conducted at recruitment and every 4 weeks until delivery. In addition, women were randomized to treatment or placebo and to three different medication administration times. The earlier trial[64] analyzed data from 100 women enrolled between 1994 and 1996, and the more recent trial[59] analyzed data from 350 women enrolled from 1997 to 2002. The incidence of preeclampsia in the control group was 14 percent for the earlier study and 13 percent for the later study. Both studies found evidence of an effect of the timing of aspirin administration on blood pressure and, in the more recent study, significant effects of aspirin on preeclampsia, IUGR, preterm birth, and any serious adverse outcome. The timing of administration was influential on the findings, with significant differences most pronounced when aspirin was taken either 8 hours after awakening, or most effectively, at bedtime.

Smaller Trials With Pregnancy or Medical History Risk Populations

In Israel, a good-quality trial by Caspi et al (1994) randomized women pregnant with twins to 100 mg aspirin beginning from 15 to 23 weeks' gestation until delivery (n=47).[61] All pregnant women with uncomplicated twin pregnancies were considered eligible for enrollment unless they had a history of chronic renal, cardiovascular, pulmonary, or hepatic disorders; past or present coagulopathy or peptic ulcers; gestational diabetes; or a known hypersensitivity to aspirin. The

protocol obtained a population of women with preeclampsia incidence of 8.7 percent in the control group and no cases in the treatment group.

A fair-quality Finish trial by Viinikka et al (1993) randomized pregnant women with preexisting hypertension or a history of severe preeclampsia in a previous pregnancy to 50 mg aspirin beginning from 15 to 16 weeks of gestation until delivery (n=208).[68] Exclusion criteria were not clearly specified. Study authors reported an incidence of preeclampsia in 9.3 percent of women treated with aspirin and 11.0 percent of women taking placebo.

An Italian trial (n=33) by Benigni et al (1989) recruited pregnant women with chronic hypertension or a history of fetal death due to placental insufficiency, severe IUGR, or early onset preeclampsia (<32 weeks) in a previous pregnancy (n=33).[60] Women with antiphospholipid antibodies present were excluded. Trial participants were randomized to receive 60 mg of aspirin or a matching placebo starting at 12 weeks' gestation until delivery. Women with chronic hypertension were treated with 50 mg of atenolol or atenolol plus 75 mg hydralazine to ensure that their diastolic blood pressure remained below 90 mm Hg. Only the incidence of gestational hypertension was reported, not rates of preeclampsia.

In Australia, a fair-quality trial by Gallery et al (1997) randomized pregnant women with preexisting chronic hypertension or renal disease, or a history of preeclampsia in a previous pregnancy to receive 100 mg of aspirin beginning during 17 to 19 weeks of gestation until 2 weeks prior to the planned delivery date (n=108).[62] Women with a history of an allergy to aspirin, aspirin-sensitive asthma, preexisting bleeding issues, or having a multifetal pregnancy were excluded. Incidence of preeclampsia was not reported; however, key indicators of preeclampsia were reported including rates of high systolic blood pressure (>140 mm Hg), uric acid (>3.5 mmol/L), and proteinuria (>300 mg/day). Leslie et al (1995) reported additional data on neonatal outcomes and was considered as an ancillary article to Gallery et al (1997).[80]

Smaller Trials Employing a Clinical Screening Test to Determine Study Eligibility

A trial by Schiff et al (1989) conducted in Israel randomized white Jewish women with nulliparity, twin gestation, or a history of preeclampsia in addition to a positive rollover test at 28 or 29 weeks' gestation to 100 mg aspirin or placebo.[66] Women with chronic hypertension were excluded. The rollover test consisted of multiple side-lying blood pressure measurements to establish a baseline, and then having the woman roll to a back-lying position and taking measurements at 5 and 5.5 minutes. A rise in the 15 mm Hg diastolic blood pressure from baseline was considered a positive rollover test. A trial in The Netherlands by Wallenburg (1986) randomized women to 60 mg aspirin from 28 weeks' gestation until delivery (n=46).[70] The study enrolled women with uncomplicated pregnancies and no history of cardiovascular or renal disease who screened sensitive to angiotensin II infusion. Sensitivity was defined as an effective pressor dose (minimum infusion of angiotensin II that resulted in a 20 mm Hg diastolic blood pressure rise) less than 10 ng/kg/m. The incidence of preeclampsia in the control group was 22.6 percent and aspirin was found to significantly reduce preeclampsia ($p<0.05$).

A fair-quality Finish trial by Villa and colleagues (n=152) recruited pregnant women at their first ultrasound screening presenting with at least one of the following risk factors: age younger than 20 or older than 40 years; BMI greater than 30 kg/m^2; chronic hypertension; a diagnosis of Sjorgren's syndrome or lupus; or a history of gestational diabetes, preeclampsia, small for gestational age, or fetal death.[69] In addition to these risk factors, women were considered for inclusion if a second-degree diastolic notch was present on transvaginal color Doppler ultrasound at 12 to 13 weeks. Participants were randomized to receive 100 mg of aspirin or placebo starting at 12 to 13 weeks of gestation through 35 weeks (or delivery if preceding 35 weeks). The incidence of preeclampsia in women taking aspirin was less than in women taking placebo, though the difference was not significant (13.1 vs. 18.3%; RR, 0.7 [95% CI, 0.3 to 1.7]).

In the United Kingdom, McParland et al (1990) randomized pregnant women with repeat abnormal Doppler waveforms at 24 weeks of gestation to 75 mg aspirin or placebo until delivery (n=106).[65] Women with a known allergy to aspirin, gestational diabetes, peptic ulcers, lupus, or a history of bleeding disorders were excluded from the trial. Preeclampsia was reported in significantly more women taking placebo compared with those taking aspirin (19% vs. 2%; p<0.02).

A fair-quality Finish trial by Vainio and colleagues (2002) recruited pregnant women at risk of preeclampsia or IUGR attending antenatal clinics who were found to have a bilateral diastolic notch on ultrasound screening at 12 to 14 weeks of gestation (n=86).[67] Women with a history of asthma, peptic ulcers, or an allergy to aspirin were excluded. In addition, if participants had used prostaglandin inhibitors within 10 days prior to recruitment they were not considered for inclusion to the trial. Participants were randomized to receive 0.5 mg/kg daily (mean, 49 mg/day per calculation) of aspirin or placebo starting at 12 to 14 weeks of gestation through delivery. Rates of preeclampsia were reported to be significantly higher in women taking placebo compared with women taking aspirin (23.3% vs. 4.7%; RR, 0.02 [95% CI, 0.05 to 0.86]).

Studies for Evaluation of Harms

To address KQ 3, we included trials of aspirin use in pregnant women regardless of their risk of preeclampsia. The trials described above for KQs 1 and 2 were also included for KQ 3. The key question additionally included four trials of low-dose aspirin use for healthy nulliparous women,[72-74,76] and one with a general population of women presenting to a hospital in Barbados for prenatal care.[75] In total, adding these five trials, there were 19 RCTs available for analysis of harms, although not all collected data for each outcome. We also identified two observational cohort studies[77,78] that met inclusion and quality criteria; one examined the effect of any aspirin exposure during pregnancy on risk of miscarriage and the other on rates of cryptorchidism among male infants.

A good-quality study by Sibai et al (1993) randomized healthy, nulliparous women between 13 and 25 weeks' gestation at seven sites in the United States (n=3,135).[72] A run-in was conducted before allocating eligible participants to 60 mg daily of aspirin or identical placebo to be taken until the time of delivery. Nearly half of the participants began treatment before 20 weeks' gestation. A majority of the women were from minority racial and ethnic backgrounds; half of

the study participants were black and nearly one third were Hispanic women. Slightly more women were lost to followup in the aspirin group (5.4% vs. 4.2%). The harms included for pooled analysis were placental abruption, intracranial fetal bleeding, and postpartum hemorrhage. In addition, other blood loss related outcomes and adverse events were reported. The incidence of preeclampsia was 6.3 percent in the control group.

A good-quality 28-site study (Subtil 1993) conducted in France and Belgium randomized 3,294 healthy nulliparous women without contraindications to 100 mg aspirin or identical placebo between 14 and 20 weeks' gestation.[74] Participants were instructed to stop taking the medication at 34 weeks' gestation. Although 16 percent of participants stopped study treatment, there were no differences in the reasons for withdrawal by study group and there was minimal loss to followup. Results on abruption, hemorrhage, and neonatal intraventricular bleeding were available for pooled analysis. The incidence of preeclampsia in the control group was very low (1.6%).

A good-quality, large single-site study in Barbados (Rotchell 1998) randomized healthy pregnant women between 12 and 32 weeks of gestation to receive 75 mg of aspirin or placebo through delivery (n=3,647).[75] Women with an increased risk of bleeding, a known allergy to aspirin, a previous history of placental abruption, or a high likelihood of immediate delivery were excluded from the trial. It was reported that 42 percent of women took their assigned medication more than 95 percent of the time during the study period. Results on abruption, perinatal mortality, and hemorrhage were available for pooled analysis. The incidence of preeclampsia in the control group was low (2.5%).

In the United States, Hauth and colleagues (1993) randomized nulliparous women in Alabama age 28 years or younger to receive 60 mg of aspirin or placebo starting at 23 weeks until delivery (n=606).[73] Participants were predominantly black (approximately 72%), with an average age of approximately 20 years. Women with a history of comorbidities that are known to increase the incidence of preeclampsia or gestational hypertension (e.g., renal disease, diabetes mellitus, multifetal gestation, chronic hypertension) were excluded from the trial. Results on abruption and perinatal mortality were available for pooled analysis. The incidence of preeclampsia in the control group was reported to be 5.6 percent.

A fair-quality trial in the United Kingdom (Davies 1995) randomized healthy nulliparous women to receive 75 mg of aspirin or a matching placebo starting at 18 weeks of gestation until delivery (n=122).[76] Women with multifetal gestations, diabetes mellitus, recurrent spontaneous abortions, or any contraindication to aspirin were excluded from the trial. Results on abruption and perinatal mortality were available for pooled analysis. The incidence of preeclampsia in the control group was reported to be 11.7 percent.

Appendix F Figure 1. Funnel Plot of Perinatal Mortality With Pseudo 95% Confidence Limits (All Trials)

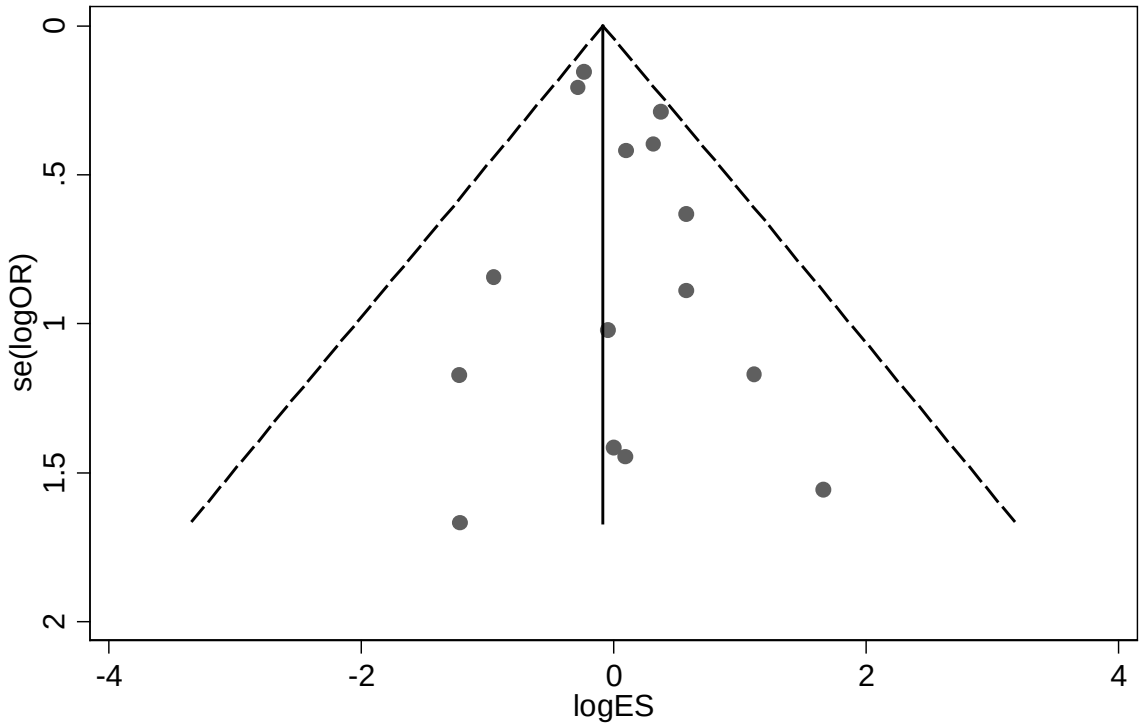


Figure 2. Sensitivity Analysis of Perinatal Mortality Sorted by Sample Size (All Trials), Removing IUGR-Only Participants

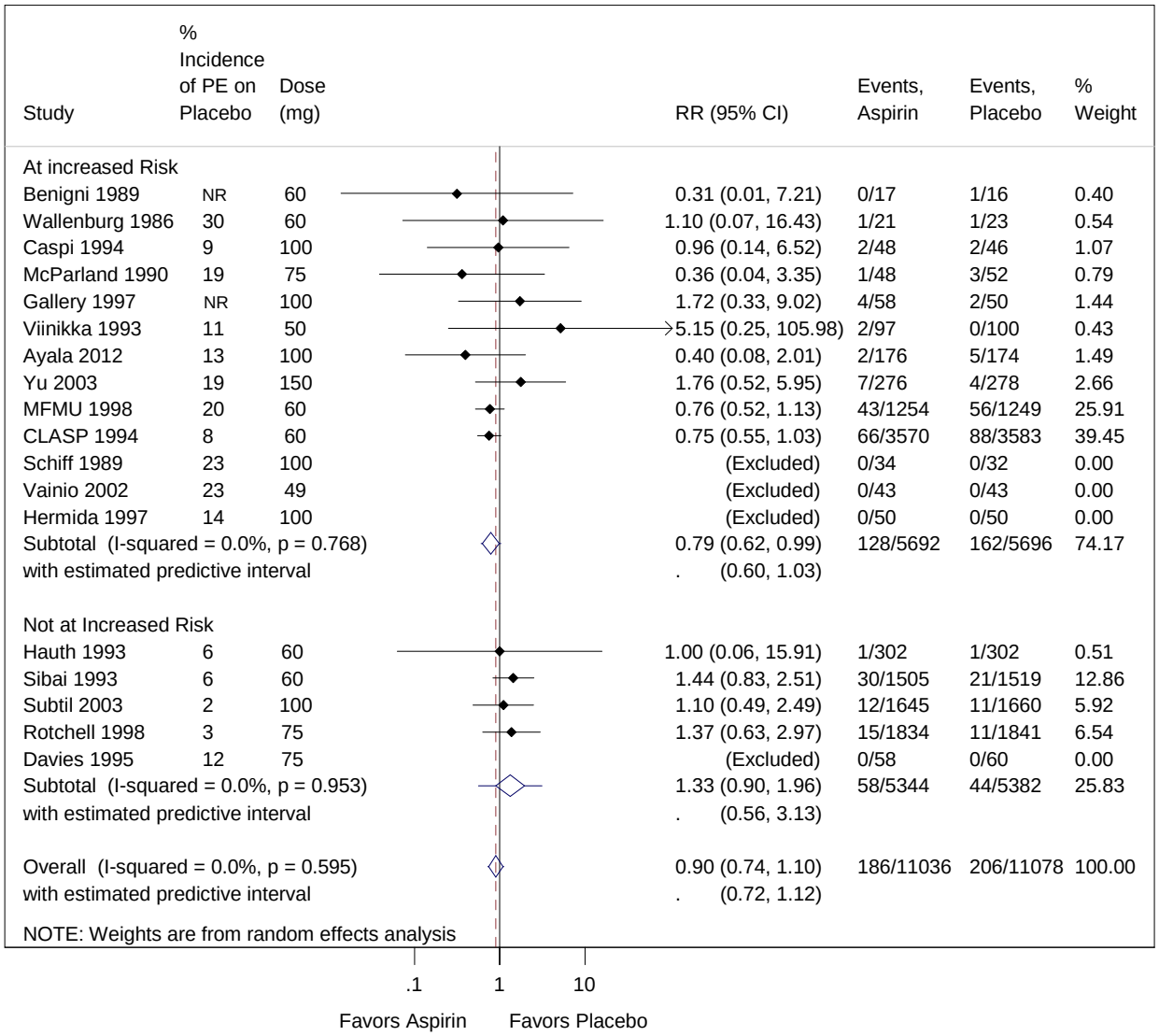


Figure 3. Sensitivity Analysis of IUGR Stratified by Initiation Week (Trials of Women at Risk of Preeclampsia [MFMU Not Included])

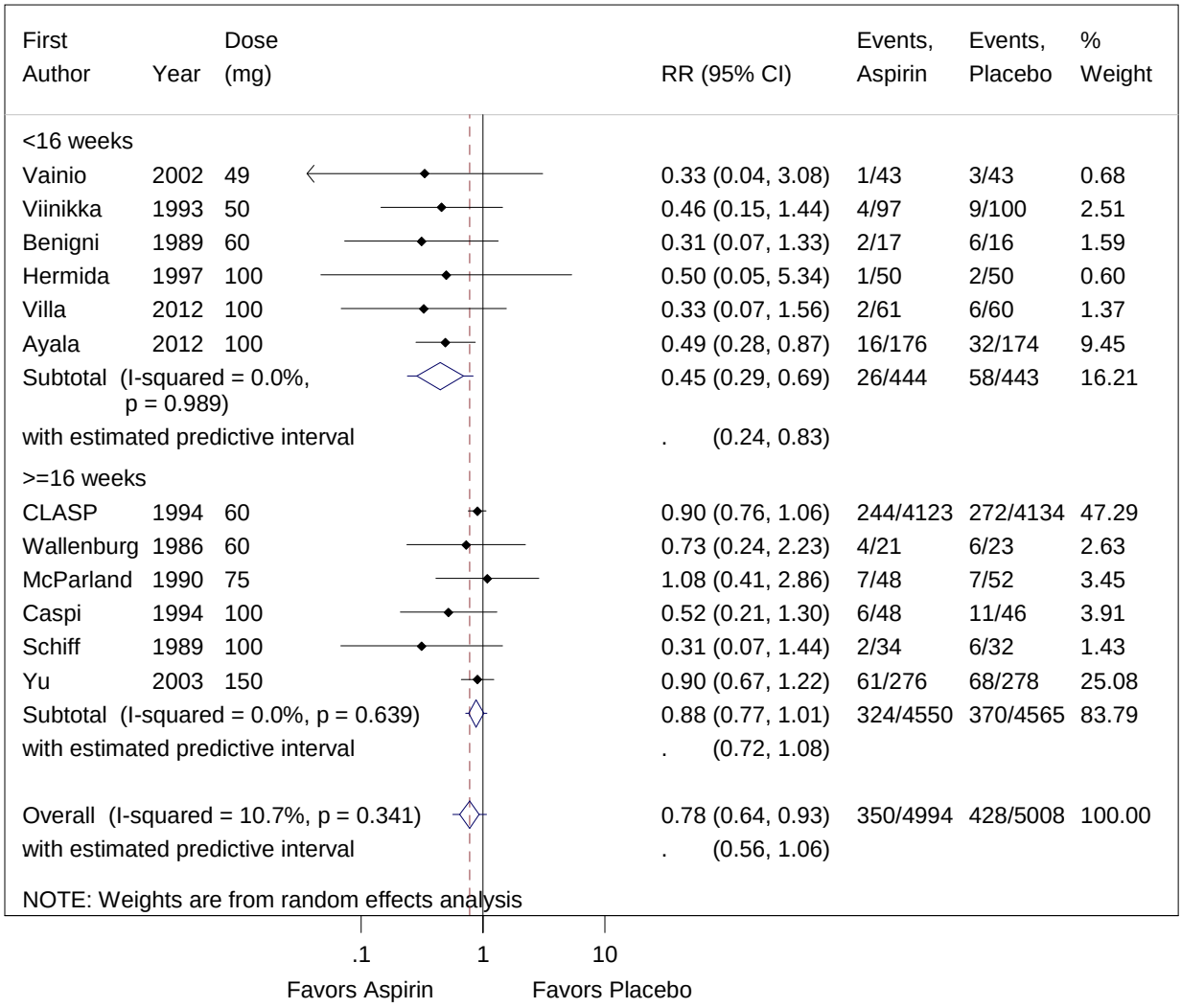


Figure 4. Funnel Plot for IUGR With Pseudo 95% Confidence Limits (Trials of Women at Risk of Preeclampsia)

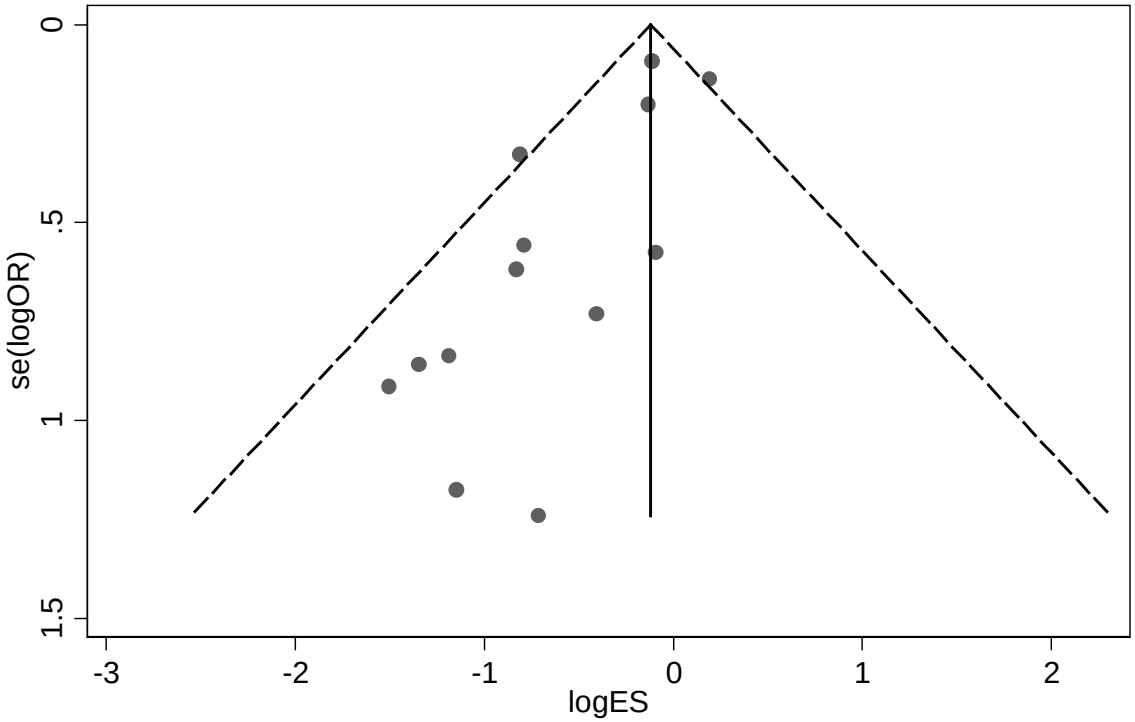


Figure 5. Funnel Plot for Preterm Birth With Pseudo 95% Confidence Limits (Trials of Women at Risk of Preeclampsia)

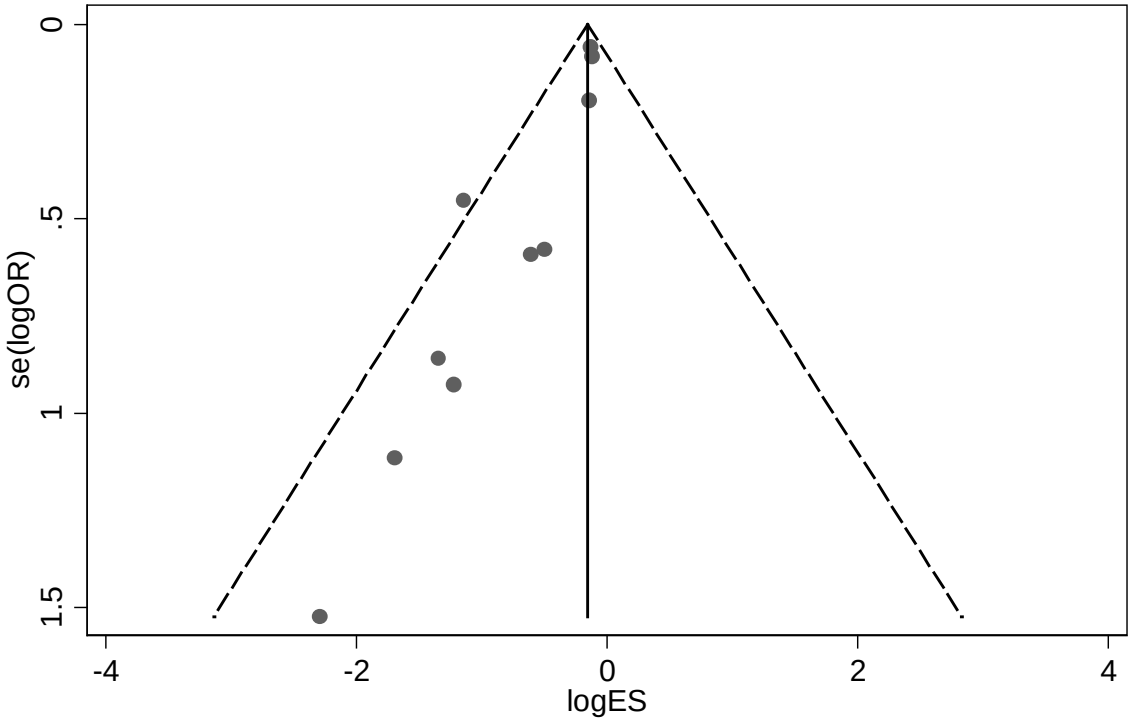


Figure 6. Funnel Plot for Preeclampsia With Pseudo 95% Confidence Limits (Trials of Women at Risk of Preeclampsia)

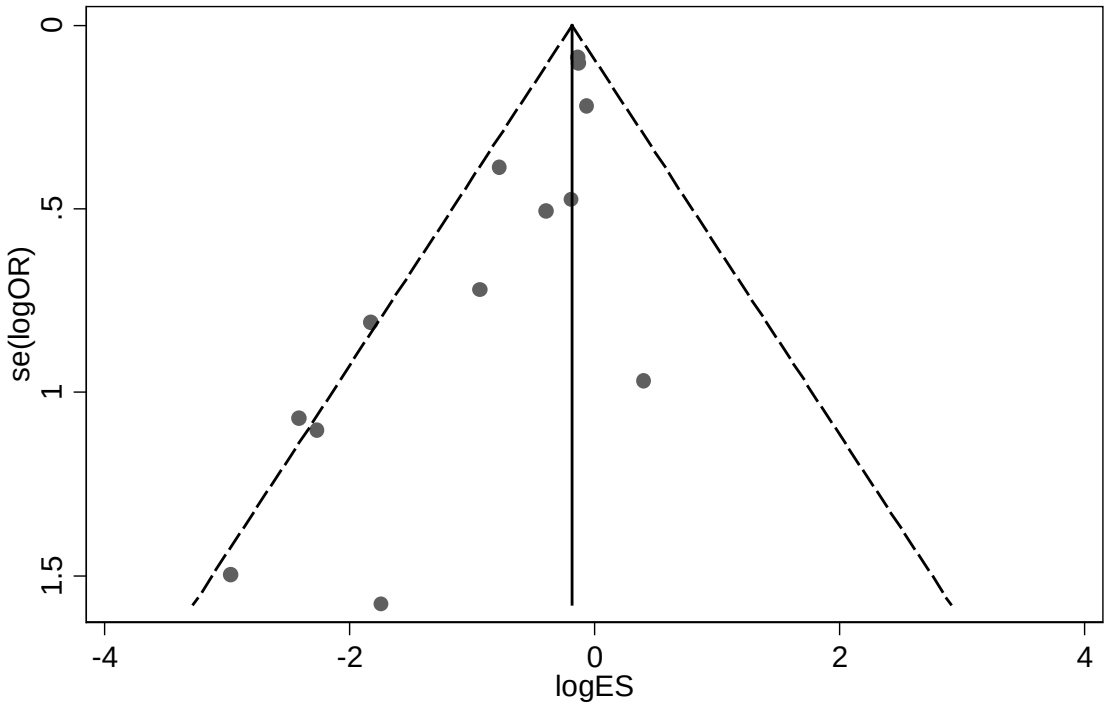


Figure 7. Pooled Analysis of Preeclampsia Sorted by Initiation Week of Treatment

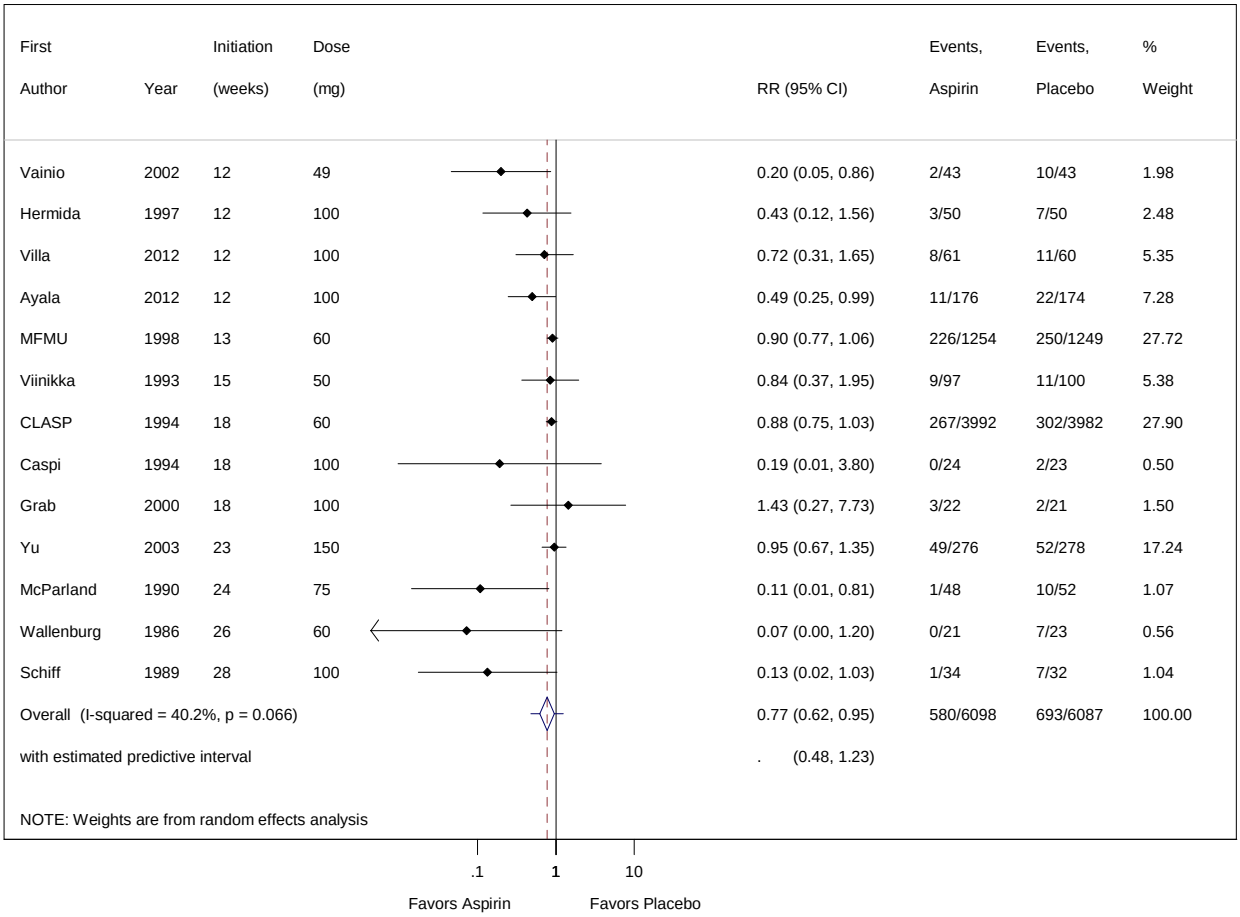


Figure 8. Pooled Analysis of Preeclampsia Sorted by Dose of Aspirin (Trials of Women at Risk of Preeclampsia)

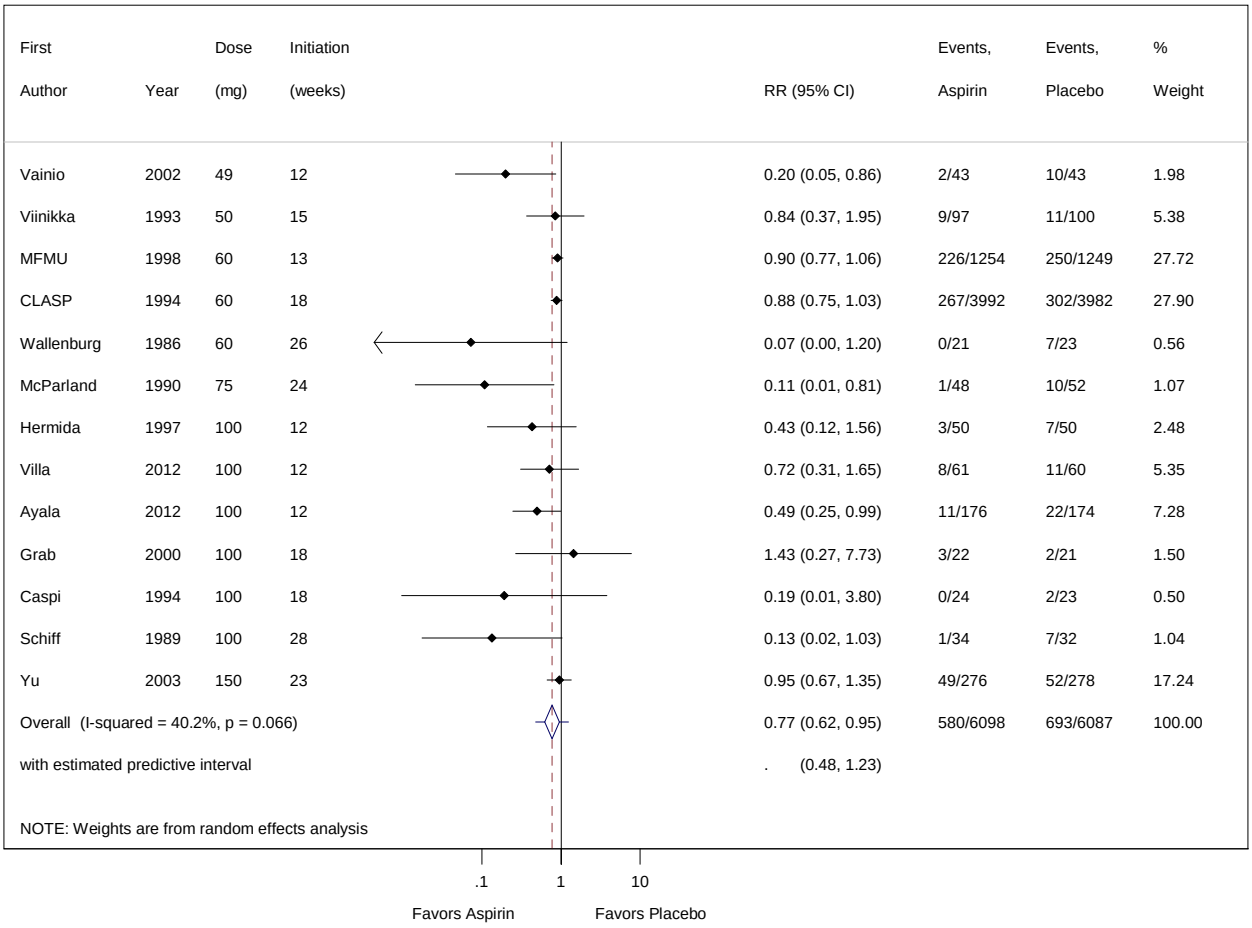


Figure 9. Pooled Analysis of Perinatal Mortality Stratified by Risk Category (All Trials)

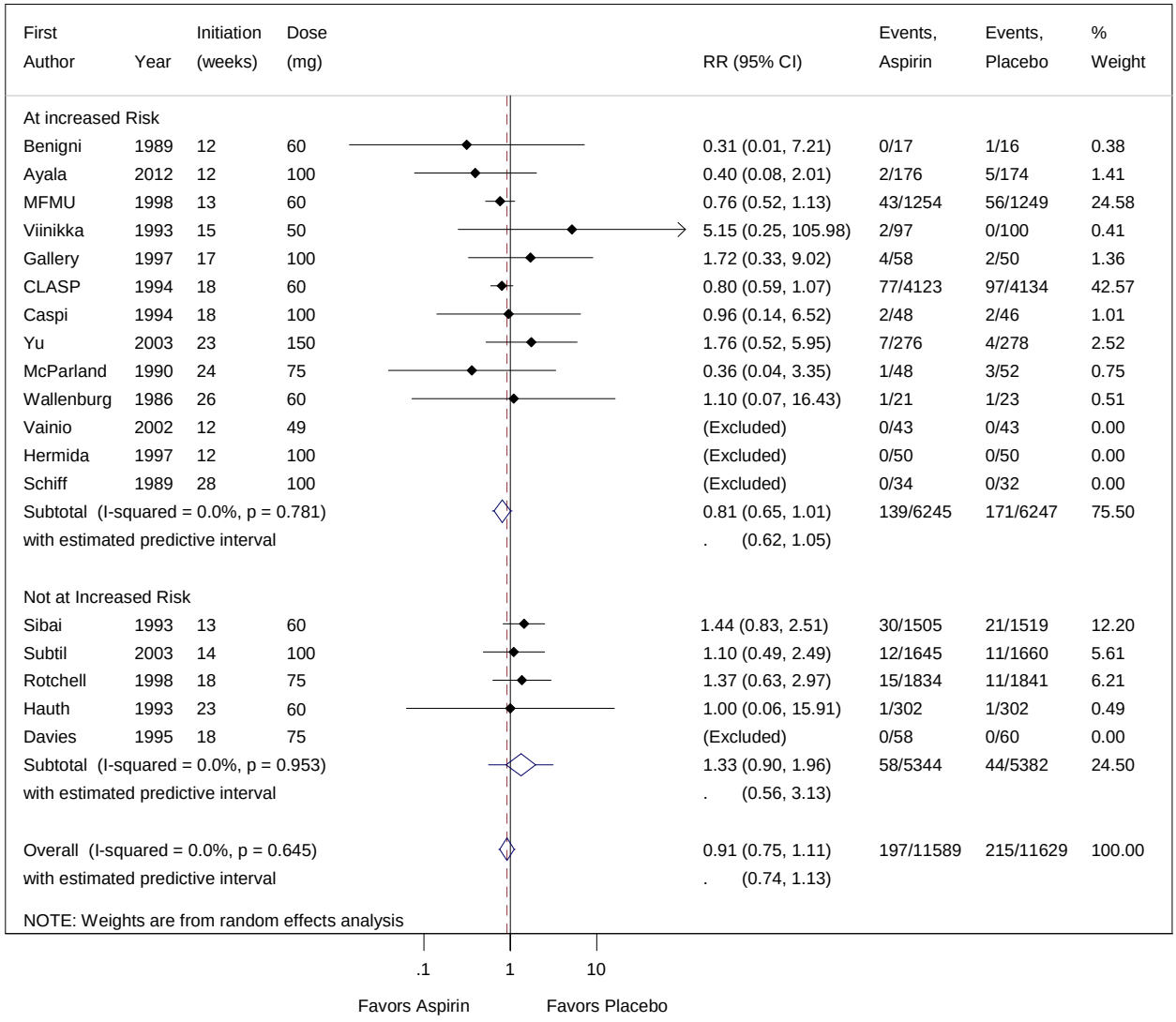


Figure 10. Pooled Analysis of Abruption Stratified by Risk Category (All Trials)

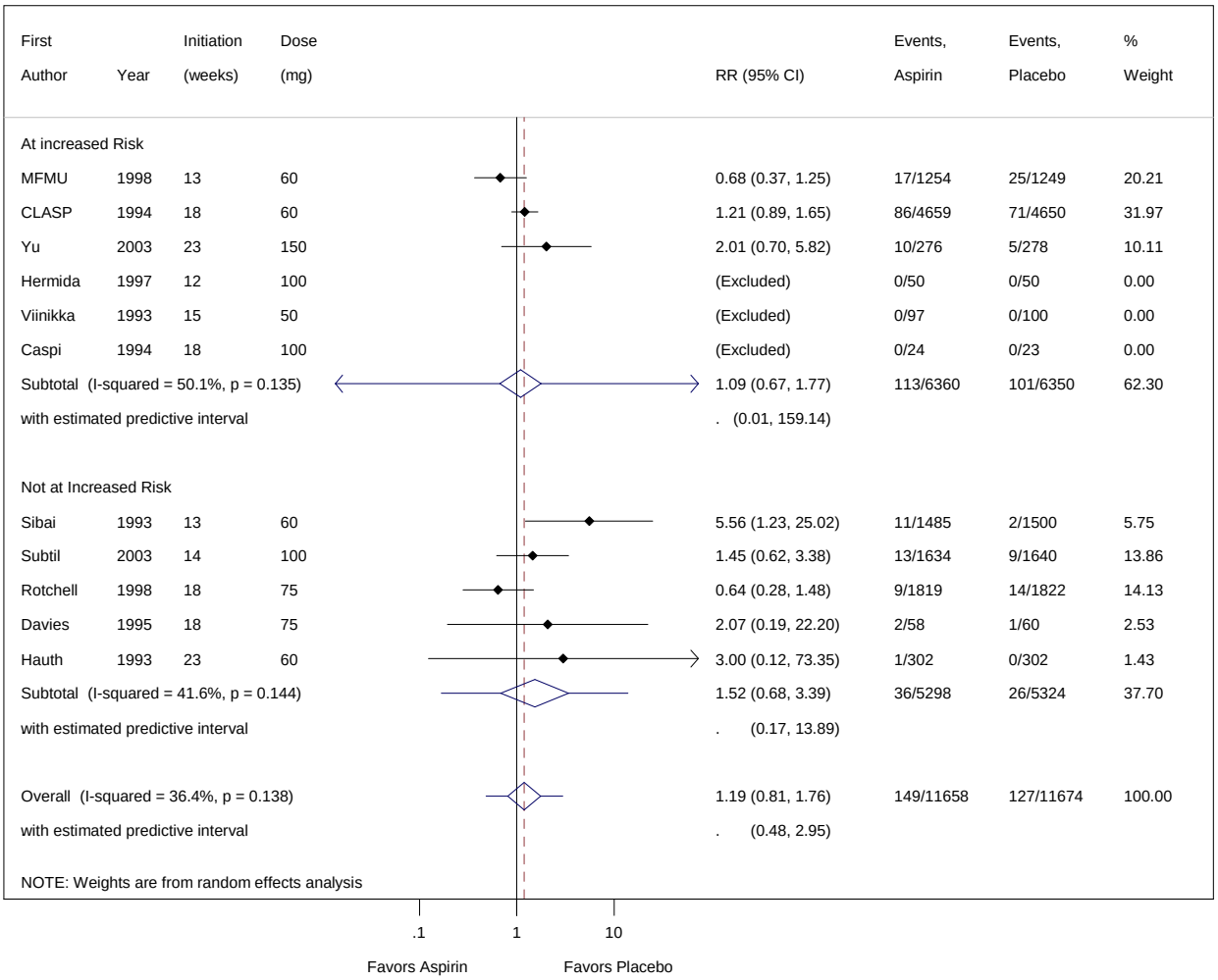


Figure 11. Pooled Analysis of Abruption Stratified by Aspirin Dose (All Trials)

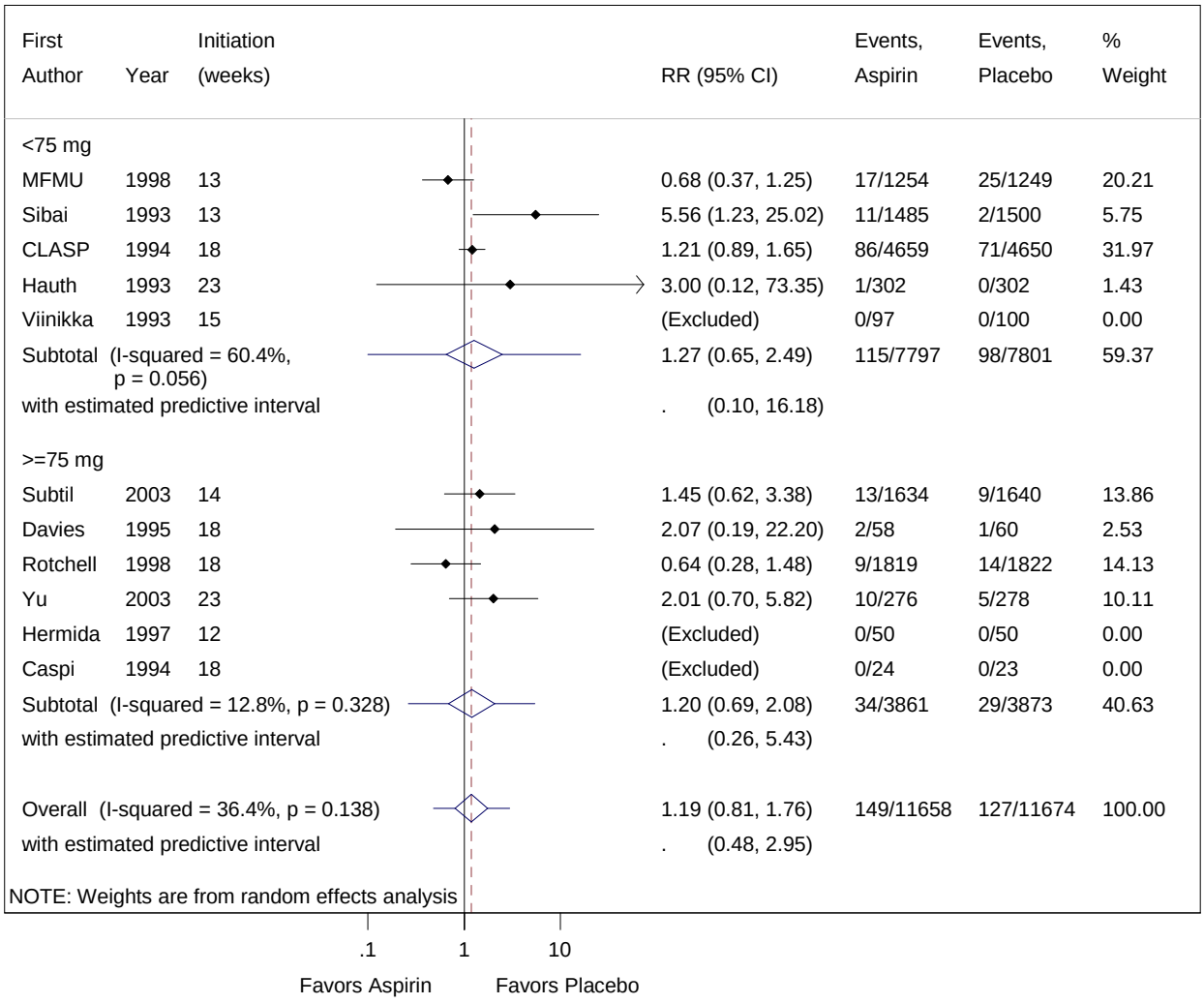


Figure 12. Pooled Analysis of Abruption Stratified by Initiation Week of Treatment (All Trials)

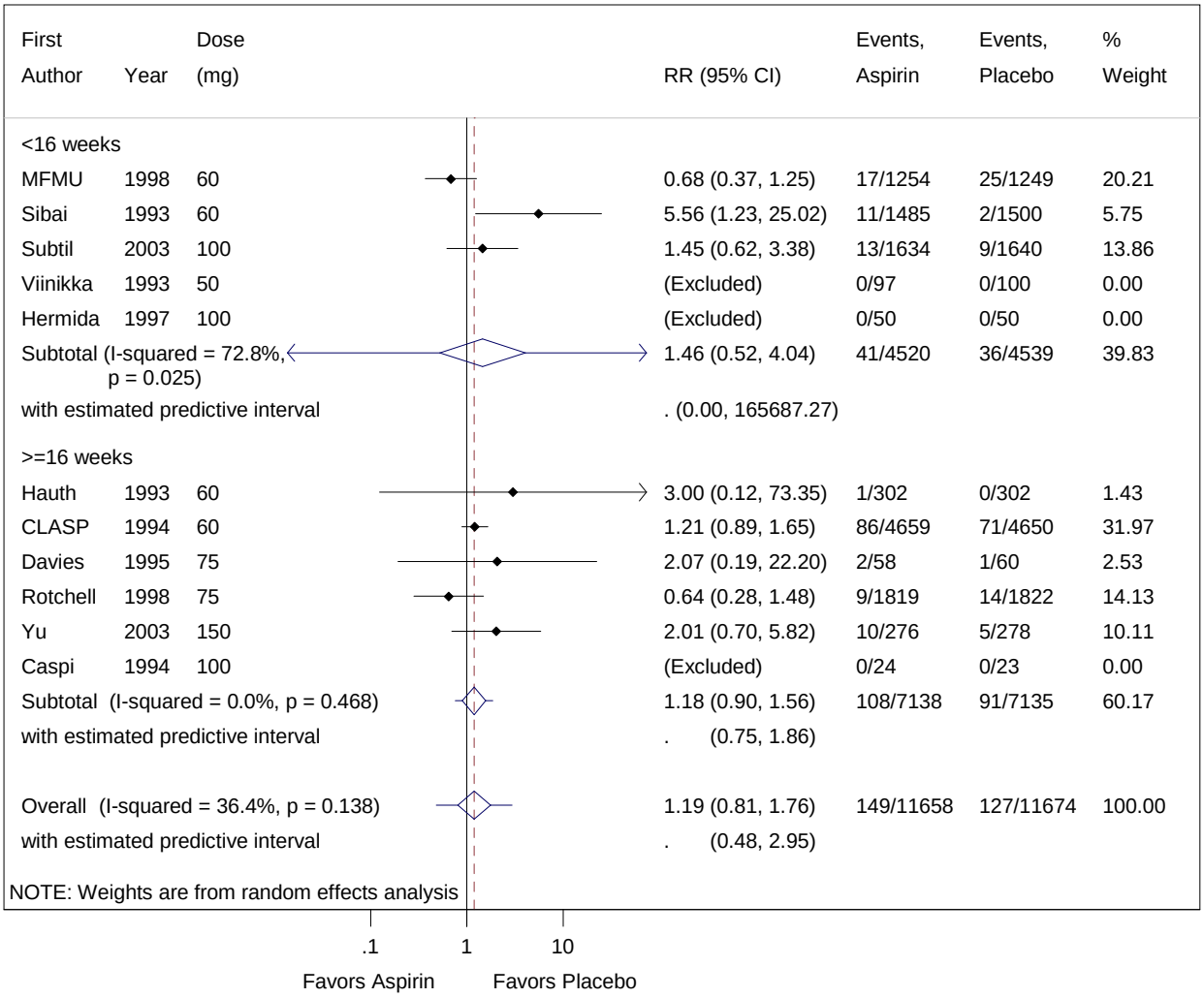


Figure 13. Sensitivity Analysis of Preeclampsia Sorted by Sample Size (Trials of Women at Risk of Preeclampsia), Removing IUGR-Only Participants

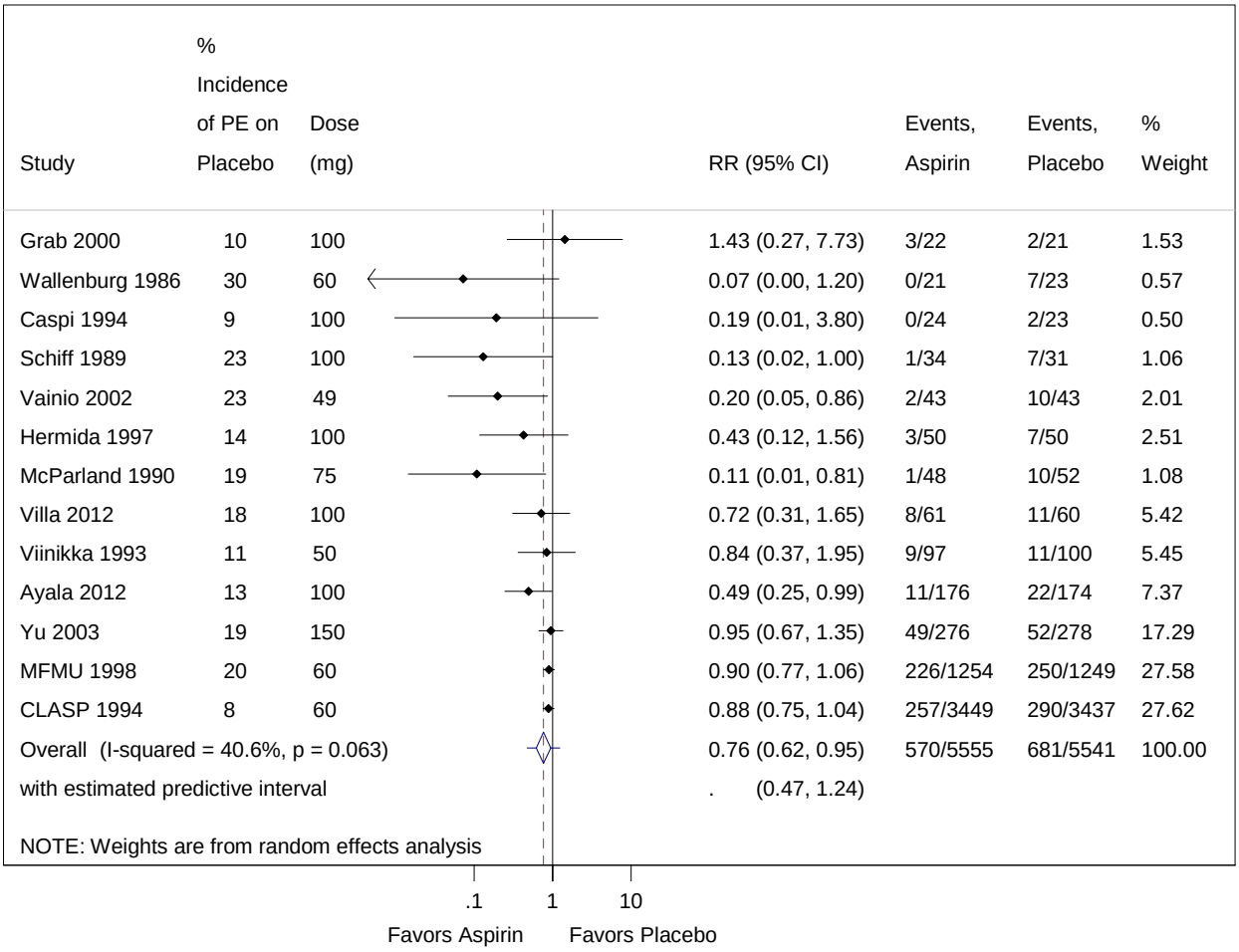


Figure 14. Sensitivity Analysis of Preterm Birth Sorted by Sample Size (Trials of Women at Risk of Preeclampsia), Removing IUGR-Only Participants

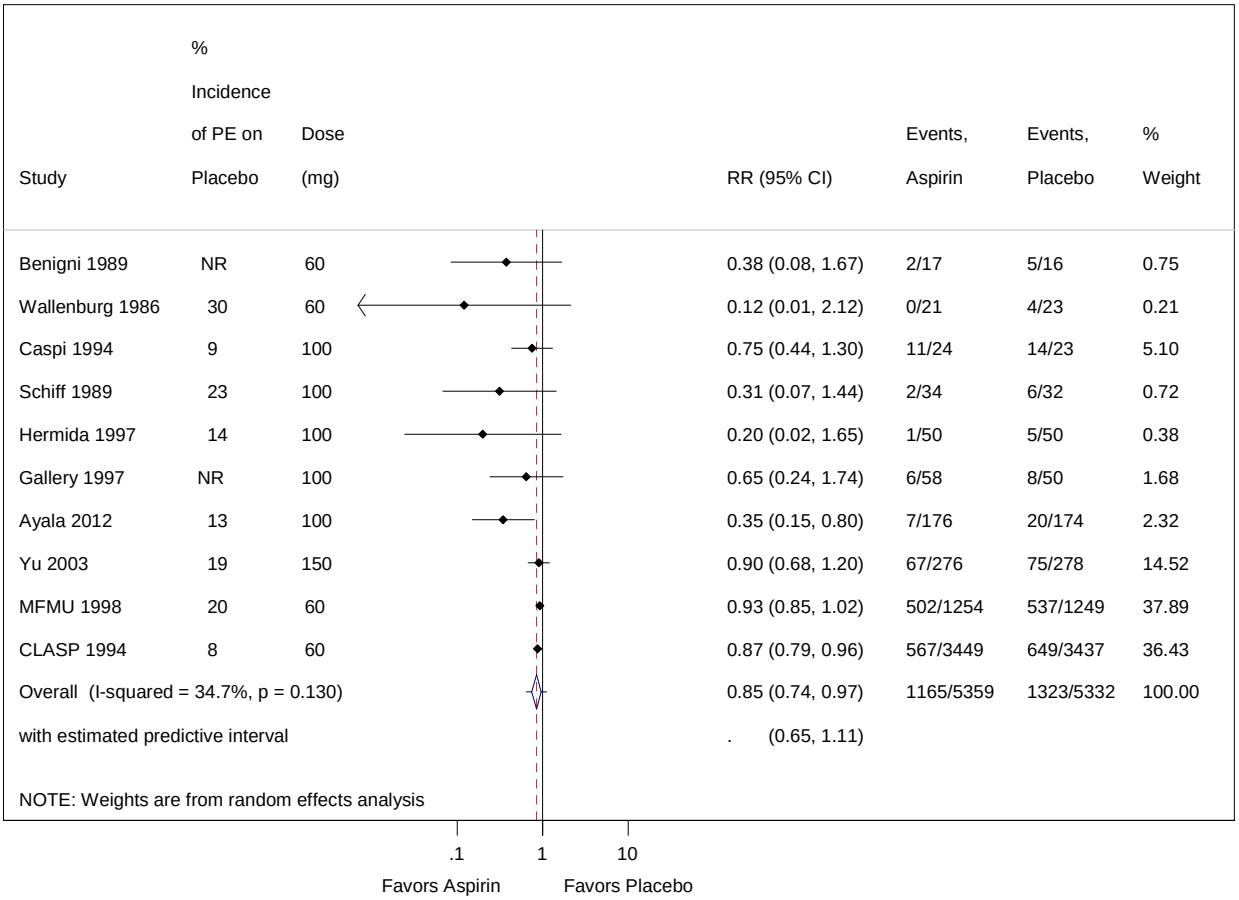
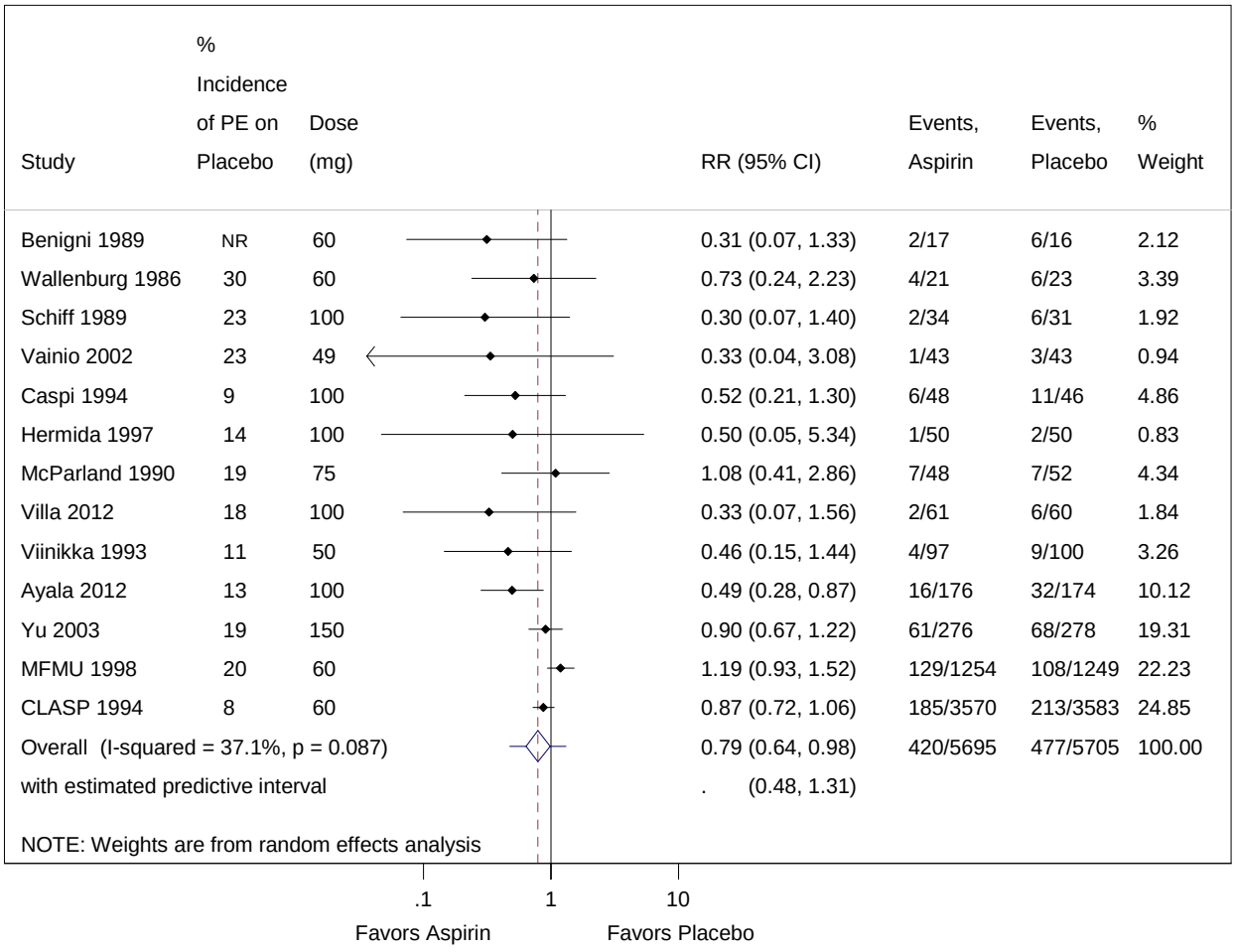


Figure 15. Sensitivity Analysis of IUGR Sorted by Sample Size (All Trials), Removing IUGR-Only Participants



Appendix G. Summary of Race/Ethnicity Subpopulation Results From Included Studies

Study, Year Quality	N analyzed	Country	Race and ethnicity, %	Race and ethnicity analyses reported in study	Incidence of preeclampsia in control group, %
Gallery, 1997[62] Fair	108	Australia	***White, NonHispanic*** IG: 96.0 CG: 95.0	No specific race and ethnicity subgroup analysis. IG and CG were comparable in composition with regard to race, age, parity, and underlying condition at start of treatment.	NR
McParland, 1990[65] Fair	100	UK	***White, NonHispanic*** IG: 73.0 CG: 65.0 ***Black*** IG: 17.0 CG: 23.0 ***Asian*** IG: 4.0 CG: 10.0 ***Other*** IG: 6.0 CG: 2.0	No specific race and ethnicity subgroup analysis.	19.2
MFMU, 1998[57] Good	2,503	US	***White, NonHispanic*** Diabetes: 53.0 HTN: 27.0 Multifetal gestations: 32.0 Previous PE: 25.0 ***Black*** Diabetes: 39.0 HTN: 61.0 Multifetal gestations: 50.0 Previous PE: 71.0 ***Hispanic*** Diabetes: 7.0 HTN: 12.0 Multifetal gestations: 18.0 Previous PE: 4.0	PE incidence by race: White (n=814) IG: 18% CG: 22% RR: 0.8 (0.6,1.1) Nonwhite (n=1,689) IG: 18% CG: 20% RR: 0.9 (0.8,1.2) Study authors concluded that aspirin was ineffective in preventing preeclampsia in all four risk groups, regardless of race.	20.0
Schiff, 1989[66] Good	*Mothers* 65 *Infants* 66	Israel	***White, NonHispanic*** 100.0 (Jewish)	NA	22.6
Yu, 2003[71] Good	554	Brazil, Chile, South Africa, UK	***White, NonHispanic*** IG: 66.3 CG: 58.3 ***Black*** IG: 24.3 CG: 30.9 ***Other*** IG: 9.4 CG: 10.8	No specific race and ethnicity subgroup analysis. Race/ethnicity similar in both IG and CG (p=0.14).	18.7

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Study, Year Quality	N analyzed	Country	Race and ethnicity, %	Race and ethnicity analyses reported in study	Incidence of preeclampsia in control group, %
Davies, 1995[76] Fair HARMS ONLY	118	UK	***White (Caucasian)*** IG: 96.6 CG: 95.0	No specific race and ethnicity subgroup analysis. Study authors commented minimally on race in the discussion. Mentioned Sibai and Hauth studies, which have large proportions of black women in their study populations. Also mentioned the Davies study, which failed to demonstrate a significant benefit with prophylactic low-dose aspirin therapy in a group of nulliparous women at low risk when the only risk factor was high hemoglobin during the 2nd trimester.	11.7
Hauth, 1993[73] Good HARMS ONLY	604	US (Alabama)	***White, NonHispanic*** IG: 30.0 CG: 27.0 ***Black*** IG: 70.0 CG: 73.0	Patients in IG and CG were of similar race (p=0.42). Study authors stated, "First, although all the women in this study were medically at low risk, the fact that many were black and all were poor undoubtedly accounted for the relatively high background rate of preeclampsia. A middle-class white population would be expected to have a lower background risk of preeclampsia, and the effect of aspirin would probably be less dramatic."	5.6
Sibai, 1993[72] Good HARMS ONLY	*Mothers* 2,985 *Infants* 3,024	US	***White, NonHispanic*** IG: 17.5 CG: 18.5 ***Black*** IG: 50.4 CG: 49.2 ***White, Hispanic*** IG: 31.3 CG: 31.8	No specific race and ethnicity subgroup analysis. Demographic characteristics of IG and CG were similar at baseline.	6.3
Keim, 2006[78] Good HARMS ONLY *(Case-control study design)*	3,129	US	***White, NonHispanic*** Cases: 62.0 Controls: 66.0 ***Black*** Cases: 32.0 Controls: 28.0 ***Other*** Cases: 6.0 Controls: 6.0	Study authors stated that black women were more likely than white women to be aspirin users.	NR
Ayala, 2012[59] Good	350	Spain	NR* Composite of Mediterranean and Nordic types		12.6

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Study, Year Quality	N analyzed	Country	Race and ethnicity, %	Race and ethnicity analyses reported in study	Incidence of preeclampsia in control group, %
Benigni, 1989[60] Fair	33	Italy	NR* Italian (includes small clusters of German-, French-, and Slovene-Italians in the north and Albanian- and Greek-Italians in the south)		NR
Caspi, 1994[61] Good	47	Israel	NR* Jewish 76.4% (of which Israel-born 67.1%, Europe/America-born 22.6%, Africa-born 5.9%, Asia-born 4.2%) NonJewish 23.6% (mostly Arab) (2004)		8.7
CLASP, 1994[58] Good	*Mothers* 9,309 (all) 7,974 (prophylactic arm only) *Infants* 9,631 (all) 8,257 (prophylactic arm only)	Argentina, Australia, Belgium, Canada, Germany, Hong Kong, Israel, Malaysia, New Zealand, Russia, Spain, Sweden, Netherlands, United Arab Emirates, UK, USA	NR* Difficult to infer given that the study was conducted in multiple countries		7.6
Grab, 2000[63] Fair	43	Germany	NR* German 91.5% Turkish 2.4% Other 6.1% (made up largely of Greek, Italian, Polish, Russian, Serbo-Croatian, Spanish)		9.5
Hermida, 1997[64] Good	100	Spain	NR* Composite of Mediterranean and Nordic types		14.0
Vainio, 2002[67] Fair	86	Finland	NR* Finn 93.4% Swede 5.6% Russian 0.5% Estonian 0.3% Roma (Gypsy) 0.1% Sami 0.1% (2006)		23.3

Appendix G. Summary of Race/Ethnicity Subpopulation Results From Included Studies

Study, Year Quality	N analyzed	Country	Race and ethnicity, %	Race and ethnicity analyses reported in study	Incidence of preeclampsia in control group, %
Viinikka, 1993[68] Fair	197	Finland	NR* Finn 93.4% Swede 5.6% Russian 0.5% Estonian 0.3% Roma (Gypsy) 0.1% Sami 0.1% (2006)		11.0
Villa, 2012[69] Fair	121	Finland	NR* Finn 93.4% Swede 5.6% Russian 0.5% Estonian 0.3% Roma (Gypsy) 0.1% Sami 0.1% (2006)		18.3
Wallenburg, 1986[70] Good	44	The Netherlands	NR* Dutch 80.7% EU 5% Indonesian 2.4% Turkish 2.2% Surinamese 2%, Moroccan 2%, Caribbean 0.8% Other 4.8% (2008 est.)		30.0
Newnham, 1995[79] Good HARMS ONLY	59	Australia	NR* White 92% Asian 7% Aboriginal and other 1%		NR
Rotchell, 1998[75] Good HARMS ONLY	*Mothers* 3,641 *Infants* 3,675	Barbados	NR* Black 93.0% White 3.2% Mixed 2.6% East Indian 1.0% Other 0.2% (2000 census)		2.5
Subtil, 2003[74] Good HARMS ONLY	*Mothers* 3,274 *Infants* 3,305	France and Belgium	NR* France: Celtic and Latin with Teutonic, Slavic, North African, Indochinese, Basque minorities Belgium: Fleming 58% Walloon 31% Mixed or other 11%		1.6

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Study, Year Quality	N analyzed	Country	Race and ethnicity, %	Race and ethnicity analyses reported in study	Incidence of preeclampsia in control group, %
Jensen, 2010[77] Good HARMS ONLY *(Cohort study design)*	47,400	Denmark	NR* Scandinavian, Inuit, Faroese, German, Turkish, Iranian, Somali		NR

* Race/ethnic data not reported in the study; data presented here are from or inferred from the CIA World Factbook (https://www.cia.gov/library/publications/the-world-factbook/index.html).

Abbreviations: HTN = hypertension; NR = not reported; PE = preeclampsia.