Low-dose aspirin for the prevention of superimposed preeclampsia in women with chronic hypertension: a systematic review and meta-analysis

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OBJECTIVE: This systematic review and meta-analysis investigated whether the use of low-dose aspirin during pregnancy by women with chronic hypertension reduces the odds of superimposed preeclampsia and poor perinatal outcomes.

DATA SOURCES: In September 2021, the following sources were searched: Embase, MEDLINE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and EU Clinical Trials Register. Only human studies were included, with no time or language restrictions.

STUDY ELIGIBILITY CRITERIA: Cohort, case—control, and randomized controlled studies reporting women with chronic hypertension pregnant with a singleton were included. Eligible studies compared low-dose aspirin use during pregnancy with a control arm.

METHODS: Risk of bias was assessed using the RoB 2 and ROBINS-I tools. A meta-analysis was performed using a random-effects model, estimating odds ratios and 95% confidence and prediction intervals, and the quality of data was assessed with the GRADE approach. Heterogeneity was investigated in regard to study methodology, timing of commencement of aspirin, and the outcome of preterm preeclampsia.

RESULTS: Nine studies (3 retrospective cohort studies and 6 randomized trials) including 2150 women with chronic hypertension were included. Low-dose aspirin prophylaxis did not significantly reduce the odds of superimposed preeclampsia in the randomized controlled trials (odds ratio, 0.83; 95% confidence interval, 0.55—1.25; prediction interval, 0.27—2.56; low-quality evidence) or observational studies (odds ratio, 1.21; 95% confidence interval, 0.78-1.87; prediction interval, 0.07—20.80; very low-quality evidence). Low-dose aspirin also did not reduce the odds of preterm preeclampsia (odds ratio, 1.17; 95% confidence interval, 0.74—1.86), and early aspirin initiation had no significant impact. There was no significant effect on small-for-gestational-age neonates or perinatal mortality; however, there was a significant reduction in preterm birth (odds ratio, 0.63; 95% confidence interval, 0.45—0.89; moderate-quality evidence). The quality of the evidence is limited by heterogeneity and risk of bias.

CONCLUSION: This meta-analysis was unable to demonstrate a significant change in the odds of superimposed preeclampsia, small-for-gestational-age infants, or perinatal mortality with the use of low-dose aspirin in women with chronic hypertension. However, significant reduction in preterm birth justifies the continued use of aspirin prophylaxis. This work was prospectively registered on the International Prospective Register of Systematic Reviews (registration number CRD42021285921).

Key words: antiplatelet, aspirin, chronic hypertension, essential hypertension, perinatal morbidity, preeclampsia, pregnancy, preterm birth, small for gestational age

Introduction

Preeclampsia is a complex medical syndrome of uncertain etiology, affecting approximately 5% of pregnancies worldwide[1] and responsible for >500,000 fetal and neonatal deaths and >70,000 maternal deaths each year.[2] Previous research has identified chronic hypertension, which is present in up to 5% of pregnant women,[3] as a major risk factor for the development of preeclampsia.[4,5] National guidelines, specifically the National Institute for Health and Care Excellence (NICE) guidance[6] and the Saving Babies' Lives Care Bundle[7] in the United Kingdom, recommend that women with chronic hypertension receive low-dose aspirin

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This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42021285921; registration confirmed on November 24, 2021).

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AJOG at a Glance

Why was this study conducted?

Prophylactic low-dose aspirin is recommended in pregnancies at high risk of preeclampsia. There is conflicting evidence on its efficacy in pregnancies of women with chronic hypertension.

Key findings

Among women with chronic hypertension, low-dose aspirin prophylaxis did not significantly reduce the odds of superimposed preeclampsia in the randomized controlled trials (odds ratio [OR], 0.83; 95% confidence interval [CI], 0.55−1.25; prediction interval [PI], 0.27−2.56; low-quality evidence) or observational studies (OR, 1.21; 95% CI, 0.78−1.87; PI, 0.07−20.80; very low-quality evidence). Low-dose aspirin prophylaxis did not reduce the odds of preterm preeclampsia, and early aspirin initiation also had no significant impact. There was no significant reduction in the odds of small-for-gestational-age neonates or perinatal mortality; however, there was a significant reduction in preterm birth (OR, 0.63; 95% CI, 0.45−0.89). The quality of the data is limited by heterogeneity and risk of bias, including loss to follow-up.

What does this add to what is known?

Low-dose aspirin in pregnancy does not significantly reduce the risk of preeclampsia for women with chronic hypertension, but does reduce the risk of preterm birth.

prophylaxis from 12 weeks' gestation until delivery to reduce the risk of complications because of placental dysfunction, such as preeclampsia and preterm birth. Aspirin modulates platelet function and inflammation, and is used in an attempt to prevent or mitigate progress of pathologic processes that lead to the development of preeclampsia.

Early studies reported that the use of aspirin was associated with significant decrease in the incidence of preeclampsia[8−11]; however, this was found to be less evident in larger trials performed subsequently.[12−14] Women deemed to be at high risk of developing preeclampsia were then specifically investigated, with trials again producing conflicting results.[15,16] Heterogeneity in dosing and timing of aspirin between studies clouded the picture; some meta-analyses reported that earlier aspirin initiation significantly improved the rates of preeclampsia compared with later aspirin initiation,[17,18] although other meta-analyses of individual patient data from women with risk factors for preeclampsia found no significant differences.[19,20] Furthermore, there is evidence that earlier aspirin initiation is associated with increased effectiveness for the prevention of preterm birth and small-for-gestational-age (SGA) infants.[21] There is also continued uncertainty about appropriate dosing, leading to variation in dosage used in clinical trials, from 60 to 200 mg daily.

There is a paucity of evidence for the clinical value of aspirin prophylaxis in women with chronic hypertension, typically because of inadequately powered studies or reliance on secondary analysis. In addition, meta-analysis findings often represent pooled data from women with a variety of risk factors for preeclampsia, sometimes complicated by multiple high-risk comorbidities in the same woman; when women with chronic hypertension do receive their own subgroup analysis, this is often for the primary outcome of preeclampsia alone.

Objectives

This systematic review and meta-analysis aimed to investigate whether the use of low-dose aspirin during pregnancy by women with chronic hypertension reduces the risk of superimposed preeclampsia. In addition, the impact of aspirin on perinatal outcomes (SGA, preterm birth, and perinatal mortality) was investigated.

Methods

Eligibility criteria

Studies reporting women pregnant with a singleton pregnancy with chronic hypertension were included. Chronic hypertension was defined as: a preexisting diagnosis of chronic hypertension; using antihypertensive medication before pregnancy; or having recorded blood pressure >140/90 on 2 occasions before 20 weeks' gestation. Chronic hypertension may coexist with other illnesses such as diabetes mellitus, antiphospholipid syndrome, and renal disease, and studies including women with these conditions were not excluded from our review and analysis. Cohort, case−control, and randomized controlled trials (RCTs) were included. Case series, case reports, and conference abstracts or posters were excluded. The eligible interventions were low-dose aspirin use during pregnancy, not restricted to a specific dose, duration of treatment, or timing of use during pregnancy. Eligible studies compared the intervention group with a control arm (women receiving a placebo or not receiving aspirin during pregnancy).

Data sources and search strategy

This review was performed using the NICE Healthcare Databases Advanced Search platform to search Embase and MEDLINE, alongside a search of the Cochrane Central Register of Controlled Trials, to identify relevant published studies. To identify ongoing and unfinished studies, the following resources were searched: ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the EU Clinical Trials Register. In addition, reference lists from key studies and other relevant systematic reviews (including those found via a search of the International Prospective Register of Systematic Reviews [PROSPERO]) were reviewed.

Key search terms were chronic (or essential) hypertension, pregnancy-

induced (or maternal) hypertension, preeclampsia, and aspirin (or antiplatelet); Medical Subject Headings (MeSH) terms, keywords, and variations on the terms were used. The search strategy was reviewed by a librarian independent of the research team. Only human studies were included, and there were no time or language restrictions. Relevant studies published in non-English languages were only excluded if an adequate translation could not be produced. The search was performed in September 2021.

Study selection and data extraction

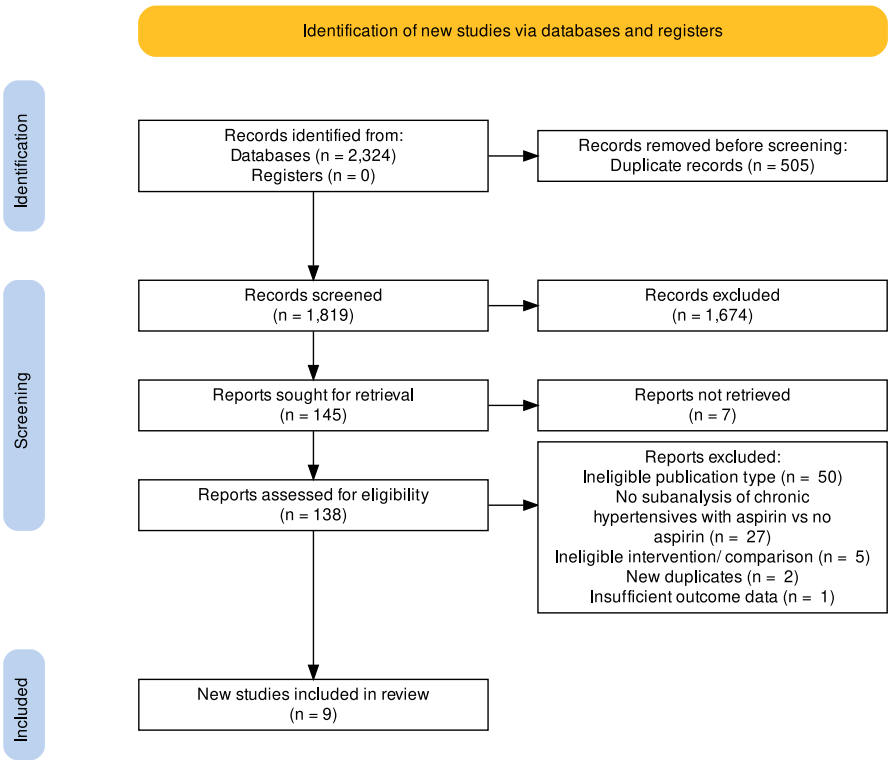
Search results' titles and abstracts were screened independently by 2 researchers (E.M.F.R. and V.G.). Articles thought to potentially address the research question were retrieved and assessed for inclusion eligibility independently by the 2 researchers. Disagreements were resolved by discussion including the third author (B.T.). In cases of multiple reports on the same cohort's data, the article with the most information presented relevant to our research question was included.

Data on study characteristics, participant characteristics, methodologies, outcomes measured, and results were manually extracted from each study by one researcher and checked by a second. Results presented for the following outcomes were extracted and tabulated for inclusion in the meta-analysis: superimposed preeclampsia, preterm preeclampsia, preterm birth, SGA, and perinatal mortality (stillbirth and neonatal mortality).

Assessment of risk of bias

Risk of bias was assessed by one researcher, and discussed with a second, using Cochrane tools: Risk of Bias 2 (RoB 2)[22] for RCTs, which categorizes risk of bias as low, of some concern, or high, and ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions)[23] for nonrandomized interventional studies, which categorizes risk of bias as low, moderate, serious, or critical. RoB 2 involves assessment of: confounding, selection of participants, intervention classification, deviations from intervention, missing data, measurement of outcomes, and selective reporting. ROBINS-I involves assessment of: randomization, deviations from intervention, missing outcome data, measurement of outcome, and selective reporting. The impact on the results of studies found to have the highest level of risk of bias was to be reviewed with a sensitivity analysis.

FIGURE 1
Flow diagram



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Data synthesis and assessment of quality of evidence

The outcomes of the studies were estimated with the odds ratio (OR) and its 95% confidence interval (CI). Meta-analyses were performed using a random-effects model, given the observed heterogeneity between studies. The results of the pooled analysis were presented as forest plots and considered significant with a P value of $<.05$.

Heterogeneity between estimates was represented with the I^2 statistic ($>40\%$ suggests considerable heterogeneity) and the 95% prediction interval (PI) for analyses including ≥ 3 RCTs. The 95% PI estimates where the true effects are to be expected for 95% of similar studies that might be conducted in the future.[24] Heterogeneity of results was investigated by analyses differentiating between study methods, timing of commencement of aspirin, and the outcome of preterm preeclampsia. When RCTs and observational studies reported the same outcome, chi-square subgroup difference testing was used to assess the differences between their findings. Heterogeneity stemming from aspirin dose could not be assessed because 3 of the 9 studies did not specify dose used; this is described in the discussion.

Fragility indices for the results of the meta-analyses of RCTs are also reported; these represent the minimum number of patients whose outcome status would have to change to turn a statistically significant result to a nonsignificant result (or vice versa).[25] Publication bias was not explored using funnel plot asymmetry tests because there were <10

TABLE 1
Characteristics of included studies

Study	Methods	Participants	Inclusion criteria	Exclusion criteria	Gestational age at entry	Intervention	Comparison	Outcomes[a]
Boriboonhirunsarn et al,[30] 2017 Thailand	Single-center, retrospective cohort, 2011–2013	300 women with cHTN	cHTN (diagnosed before pregnancy, with or without treatment)	Women with prepregnancy DM, multiple gestation, documented fetal anomalies, incomplete data	NA	Aspirin prophylaxis (undefined)	No aspirin	Superimposed PE[a], gestational age at delivery, SGA, low BW, asphyxia, and NICU admission
Byaruhanga et al,[31] 1998 Zimbabwe	Single-center RCT, double-blind, 1994–1995	250 women at high risk, of which 37 had cHTN	Previous PIH/PE/ eclampsia or cHTN	Contraindications to aspirin use; development of PE before entry in trial	20–28 wk	75-mg aspirin up to 38 wk	Placebo	PE[a], duration of pregnancy, perinatal mortality, BW
ECPPA,[32] 1996 Brazil	Multicenter RCT, double-blinded, ITT analysis, 1989–1993	1009 high-risk women, of which 473 had cHTN	Women with risk factors (eg, cHTN detected before or during pregnancy, primigravidity, DM, renal disease, a history or presence of PE or IUGR)	Women with contraindications to aspirin use, placenta previa	12–32 wk	60-mg aspirin OD (started at or after 12/40 until delivery)	Placebo	PE[a], preterm delivery (<37/40)[a], maximum maternal BP recorded after entry; crude BW (IUGR=BW <3rd centile)[a]; stillbirth (24/40+) and neonatal death[a]; maternal and fetal complications related to bleeding; blood transfusion
Lecarpentier et al,[33] 2013 France	Multicenter retrospective cohort, 2004– 2007	211 women with cHTN	cHTN (needing treatment before pregnancy)	Multiple pregnancies, secondary HTN, proteinuria at <20 wk, cHTN but without any treatment at first prenatal visit, women transferred from other maternity units, fetal malformations	NA	LDA (undefined)	No aspirin	Superimposed PE[a], FGR (BW <5th centile), placental abruption, HELLP syndrome

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TABLE 1
Characteristics of included studies *(continued)*

Study	Methods	Participants	Inclusion criteria	Exclusion criteria	Gestational age at entry	Intervention	Comparison	Outcomes[a]
Lin et al,[34] 2021 China (Preproof)	Multicenter single-blind RCT, 2016−2019	990 high-risk women randomized, of which 441 had cHTN	18−55 years, singleton pregnancy, live fetus at the gestational age of 12−20 wk; high risk, ie, history of PE, DM (type 1 or 2), or cHTN; or ≥2 intermediate risk factors: obesity, advanced maternal age (≥35 y), family history of PE, or nulliparity	Contraindications to aspirin use, autoimmune diseases; mental disorders; history of alcohol or drug abuse within 6 mo; in vitro fertilization; previous registration in another drug trial within the previous 3 mo	< 20 wk	100-mg aspirin, initiated from 12−20 wk until 34 wk	No aspirin	PE[a], PE delivery before 34 wk, before 37 wk, and at or after 37 wk of gestation[a]; gestational HTN; HELLP syndrome; placental abruption; PPH, fetal distress, PTB; miscarriage, stillbirth, or neonatal death; fetal death with PE; perinatal death; fetal malformation; low BW; very low BW; SGA; Apgar score and NICU admission
McCowan et al,[35] 1996 New Zealand	Single-center retrospective cohort, 1991−1993	155 pregnancies in women with cHTN	dBP ≥90 before 20 wk or preexisting diagnosis of essential HTN and on antihypertensive medicines	Evidence of secondary causes of HTN	NA	75-mg aspirin commenced at <20 wk	No aspirin	Superimposed PE[a], perinatal loss, SGA (BW <5th centile)[a], PTB (before 37 and 32 wk), abruption
Moore et al,[36] 2015 United States	Secondary analysis of Caritis et al,[15] 1998; multicenter double-blind RCT 1991−1995	523 high-risk women, of which 186 had cHTN	Women with cHTN (on treatment or BP ≥140/90 before pregnancy or before 20 wk), DM, history of PE	Multifetal gestations, history of PE with current proteinuria	<17+0 wk	60-mg aspirin from recruitment until delivery	Placebo	Superimposed PE at any gestation[a], early PE (before 34/40)[a], late PE (34/40+)[a], SGA (BW <10th centile)[a], compositie early PE or SGA[a]
Poon et al,[37] 2017 United Kingdom, Spain, Italy, Belgium, Greece, Israel	Multicenter, double-blind RCT (Secondary analysis of ASPRE)[16]	1776 women assigned, of which 110 had cHTN	≥18 years, no serious mental illness or learning difficulties, singleton live pregnancy, no major abnormality demonstrated, estimated risk for preterm PE of >1 in 100 (including history of cHTN as reported by participants)	(not specified)	At the 11−13 wk visit	150-mg aspirin, administered from 11−14 wk until 36 wk	Placebo	Delivery with superimposed PE <37 wk[a]

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TABLE 1
Characteristics of included studies *(continued)*

Study	Methods	Participants	Inclusion criteria	Exclusion criteria	Gestational age at entry	Intervention	Comparison	Outcomes[a]
Xiang et al,[38] 2020 China	Multicenter RCT, 2018–2019	393 women with mild to moderate cHTN	Mild to moderate cHTN (SBP, 140–159; dBP, 90–109) documented between 6 and 10 weeks' gestation, without medication and target organ disease	Women with multiple embryos, previous proteinuria, and other conditions such as DM and asthma), and fetal defects during pregnancy	9 wk (+/- 2 wk)	LDA (undefined) from 12–36 wk	Placebo	Superimposed PE at any gestation[a], SGA (BW <10th centile)[a], premature delivery (<37 wk)[a], neonatal hypoglycemia[a], neonatal hyperbilirubinemia[a], intrauterine fetal demise[a]

BP, blood pressure; *BW*, birthweight; *dBP*, diastolic blood pressure; *DM*, diabetes mellitus; *cHTN*, chronic hypertension; *FGR*, fetal growth restriction; *HTN*, hypertension; *ITT*, intention-to-treat; *IUGR*, intrauterine growth restriction; *LDA*, low-dose aspirin; *NA*, not applicable; *NICU*, neonatal intensive care unit; *OD*, once daily; *PE*, preeclampsia; *PIH*, pregnancy-induced hypertension; *PPH*, postpartum hemorrhage; *PTB*, preterm birth; *RCT*, randomized controlled trial; *sBP*, systolic blood pressure; *SGA*, small for gestational age.

[a] Reported for women with chronic hypertension and stratified by aspirin exposure.

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studies included. All analyses were conducted with R statistical software, version 4.2.1 (R Core Team, Vienna, Austria).[26]

The overall quality of the evidence pooled for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach[27] and GRADEPro software (Evidence Prime, Kraków, Poland).[28] Evidence from RCTs was downgraded from "high quality" and evidence from observational studies was downgraded from "low quality" by 1 or 2 levels depending on severity of risk of bias, indirectness of evidence, inconsistency in estimates of effect, imprecision of effect estimates, or potential publication bias.

This systematic review and meta-analysis was registered on PROSPERO (CRD42021285921, and functioning as a protocol) before screening of the search results.[29]

Results

Study selection

Following systematic searches of databases and reference lists, we identified 1819 unique records, of which 1674 were excluded after title and abstract screening. Another 129 records were excluded following full-text review, and 7 full-text articles were not retrieved, resulting in 9 articles for inclusion in the meta-analysis (Figure 1).

Study characteristics

Of the 9 included studies, 6 were RCTs, and 3 were retrospective cohort studies (Table 1). There was a wide geographic distribution of study populations. Four studies included only participants with chronic hypertension, whereas the other 6 included women with different risk factors for preeclampsia. The sample sizes of women with chronic hypertension ranged from 37 to 473 women. The 3 retrospective cohort studies compared aspirin with no prophylaxis, as did one of the randomized trials, and placebo was used otherwise. All studies used low-dose or "prophylactic" aspirin, with dosage ranging from 60 to 150 mg once daily, although 3 studies did not

TABLE 2
Risk of bias assessments

Retrospective cohort studies	Confounding	Selection of participants	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selective reporting	Overall	Comments
Boriboonhirusarn et al,[30] 2017	Moderate	Low	Serious	Low	Low	Low	Moderate	Serious	Logistic regression adjusted for the confounders of age, parity, prepregnancy BMI, previous PE (but not comorbidities). All participants were of same ethnicity. The intervention of "ASA prophylaxis" was undefined.
Lecarpentier et al,[33] 2013	Serious	Low	Serious	Low	Low	Low	Moderate	Serious	Logistic regression to control for confounders included ethnicity, parity, previous PE (but not age, comorbidities, or BMI). The intervention of "low-dose aspirin" was undefined.
McCowan et al,[35] 1996	Serious	Low	Low	Low	Low	Low	Moderate	Serious	Some potential confounders controlled for in relation to SGA outcome, but not described for PE.
Randomized trials			**Randomization**	**Deviations from intervention**	**Missing outcome data**	**Measurement of outcome**	**Selection of reported result**	**Overall**	**Comments**
Byaruhanga et al,[31] 1998			Low	Low	Some concerns	Low	Low	Some concerns	20 of the randomized subjects (8%) lost to follow-up (12 in aspirin group, 8 in placebo group).
ECPPA,[32] 1996			Low	Low	Low	Low	Low	Low	Follow-up forms obtained for 96% of randomized women (476 allocated to aspirin, 494 to placebo)
Lin et al,[34] 2021			Low	Low	Low	Low	Low	Low	Study protocol reviewed. Registered with ClinicalTrials.gov: NCT02797249, with recruitment commencing following registration.
Moore et al,[36] 2015			Low	Low	Low	Low	Some concerns	Some concerns	Secondary analysis of Caritis et al,[15] 1998.

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TABLE 2
Risk of bias assessments *(continued)*

Retrospective cohort studies	Confounding	Selection of participants	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selective reporting	Overall	Comments
Poon et al,[37] 2017			Low	Low	Low	Low	Some concerns	Some concerns	Subgroup analyses for obstetrical history prespecified but those for maternal characteristics/ medical history were post hoc. Secondary analysis of ASPRE[16]; protocol reviewed. The ASPRE trial was registered with ISRCTN: ISRCTN13633058, with recruitment commencing following registration.
Xiang et al,[38] 2020			Some concerns	Low	Low	Low	Low	Some concerns	No information on concealment of randomization and intervention allocation. "Low-dose aspirin"—dose undefined.

ASA, acetylsalicylic acid; *BMI*, body mass index; *PE*, preeclampsia; *SGA*, small for gestational age.

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specify the dosage. In 5 studies the aspirin was commenced before 20 weeks' gestation.

Secondary outcomes were reported in 5 of the 9 studies, although there was variation in outcome definition. For example, studies defined preterm preeclampsia as either before 34 weeks gestation, before 37 weeks gestation, or before 37 weeks gestation with delivery. In addition, studies reported SGA or intrauterine growth restriction as birthweight below 3rd, 5th, or 10th centiles.

Risk of bias of included studies

Seven of the 9 studies included were found to have a source of risk of bias (Table 2). However, none of the studies were found to have "critical" risk (for cohort studies) or "high" risk (for randomized trials), and therefore none were excluded from the analysis.

Synthesis of results

A total of 1078 women affected by chronic hypertension on aspirin were compared with 1072 women with chronic hypertension on placebo (or no aspirin) during pregnancy, in separate analyses by methodology.

Table 3 summarizes the findings of the meta-analyses, including the OR and 95% confidence interval, 95% prediction interval, and fragility index. Low-dose aspirin prophylaxis did not significantly reduce the odds of superimposed preeclampsia in the RCTs (OR, 0.83; 95% CI, 0.55−1.25; PI, 0.27−2.56; low-quality evidence) (Figure 2) or observational studies (OR, 1.21; 95% CI, 0.78−1.87; PI, 0.07−20.80; very low-quality evidence) (Figure 3). Even with point estimates of the OR on either side of the null, there were no significant differences in the findings of the observational studies and RCTs (chi-square statistic, 1.47; P=.22). The quality of the evidence is limited in most of the studies by risk of bias, heterogeneity (I2 >40%), and imprecision (Figure 4). The heterogeneity is reflected in the PI, which was much wider for the observational studies than for the RCTs. The data from the RCTs were associated with a fragility index of 11, suggesting that it would take 11 outcome status changes

to turn this statistically insignificant result into a significant one, which is unfortunately smaller than the number of patients lost to follow-up within the included studies.

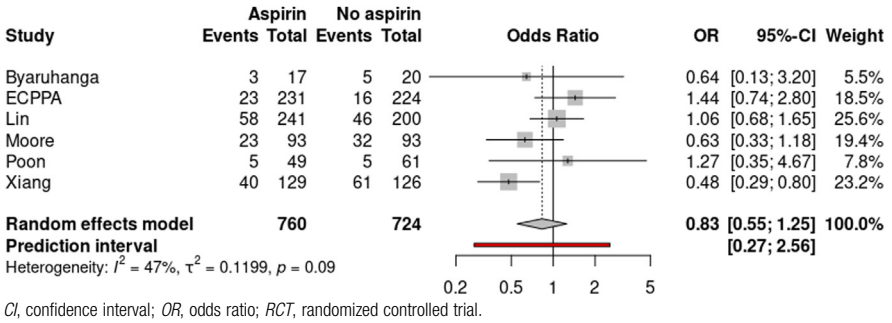
Four RCTs and 1 observational study reported that aspirin was commenced before 20 weeks' gestation. The pooled results from the RCTs with early aspirin initiation did not demonstrate a significant reduction in preeclampsia rates (OR, 0.74; 95% CI, 0.47−1.16; I2, 52%; PI, 0.14−4.05; low-quality evidence) (Figure 5). The observational study did not report a statistically significantly different OR for superimposed preeclampsia from that of the RCTs (chi-square statistic, 1.93; P=.16).

Three RCTs reported preterm preeclampsia, including 383 women on aspirin and 354 women in the control group. The pooled data also found no significant effect of low-dose aspirin (OR, 1.17; 95% CI, 0.74−1.86; I2, 0%; low-quality evidence) (Figure 6), with a wide PI (0.06−23.39); the evidence was assessed to be of low quality because of the implementation of post hoc secondary analyses of data and the few numbers of events (Figure 4).

Aspirin significantly reduced the odds of preterm birth. Two RCTs reported the number of preterm births among 360 women on aspirin and 350 women in the control group (22.2% vs 31.1%; OR, 0.63; 95% CI, 0.45−0.89; I2, 0%) (Figure 7). This was assessed to be moderate-quality evidence because 1 of the 2 studies had risk of bias, specifically in regard to lack of information on concealment of randomization, intervention allocation, and aspirin dose (Figure 4). The fragility index of 5 is much smaller than the number of patients lost to follow-up in the included studies.

Three RCTs reported SGA neonates, with an associated OR of 0.96 (95% CI, 0.65−1.40; PI, 0.08−11.53; moderate-quality evidence) in pregnant women with chronic hypertension using aspirin compared with those not using aspirin (Figure 8). Data from the observational study that reported SGA outcomes did not report a statistically significantly different OR for superimposed preeclampsia relative to the RCTs (chi-square statistic, 2.50; P=.11).

FIGURE 2
Superimposed preeclampsia (RCTs)



CI, confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial.

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Perinatal mortality, including stillbirth and neonatal deaths, was reported by 2 RCTs, including 28 of 362 (7.7%) cases in the treatment group and 28 of 352 (8.0%) cases in the placebo group (OR, 0.88; 95% CI, 0.36−2.14) (Figure 9). This was assessed to be very low-quality evidence because of risk of bias, heterogeneity (I2, 54%), and imprecision (Figure 4).

Comment

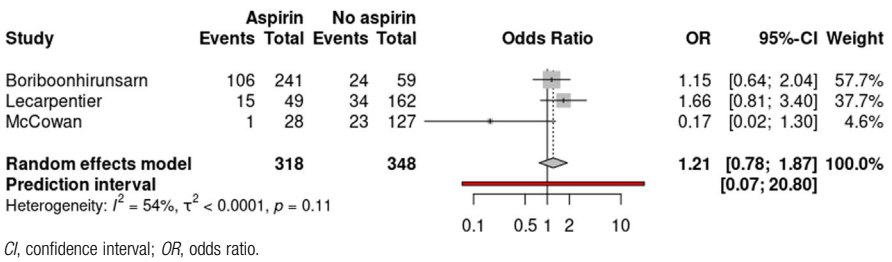
Principal findings

In this meta-analysis, we addressed an important clinical question: whether low-dose aspirin in pregnancy reduces the risk of preeclampsia and neonatal morbidity in women with chronic hypertension. We identified 9 studies including 2150 women with chronic hypertension that met our inclusion criteria, of which none were judged to be at the highest risk of bias.

Data pooled from 6 RCTs identified a reduction in the odds of superimposed preeclampsia of 17% (OR, 0.83; 95% CI, 0.55−1.25; low-quality evidence), and although this reduction did not reach statistical significance, the data suggest that the intervention is more likely to confer benefits than not. This interpretation is limited because the fragility index of 11 is lower than the number of women lost to follow-up in the included studies; there is a theoretical risk that the outcomes of those lost to follow-up could have resulted in the findings of the analysis changing considerably.

The 3 retrospective cohort studies of very low quality suggest that low-dose aspirin may be associated with an increased odds of superimposed preeclampsia in women with chronic hypertension (OR, 1.21; 95% CI, 0.78−1.87), although the PI is wide and therefore there is much uncertainty regarding what similar future studies may find. Overall, uncertainty around

FIGURE 3
Superimposed preeclampsia (cohorts)



CI, confidence interval; *OR*, odds ratio.

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FIGURE 4
Summary of findings, including GRADE assessments

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	low dose aspirin	control	Relative (95% CI)	Absolute (95% CI)	
Superimposed pre-eclampsia (RCTs)											
6	randomised trials	serious[a,b,c]	serious[d]	not serious	not serious	none	152/760 (20.0%)	165/724 (22.8%)	**OR 0.83** (0.55 to 1.25)	**31 fewer per 1,000** (from 88 fewer to 42 more)	⨁⨁◯◯ Low
Superimposed pre-eclampsia (Observational studies)											
3	observational studies	serious[e,f]	serious[d]	not serious	not serious	none	122/318 (38.4%)	81/348 (23.3%)	**OR 1.21** (0.78 to 1.87)	**36 more per 1,000** (from 41 fewer to 129 more)	⨁◯◯◯ Very low
Superimposed pre-eclampsia given early aspirin initiation											
4	randomised trials	serious[b,c]	serious[d]	not serious	not serious	none	126/512 (24.6%)	144/480 (30.0%)	**OR 0.74** (0.47 to 1.16)	**59 fewer per 1,000** (from 132 fewer to 32 more)	⨁⨁◯◯ Low
Preterm pre-eclampsia											
3	randomised trials	serious[c]	not serious	not serious	serious[g]	none	48/383 (12.5%)	37/354 (10.5%)	**OR 1.17** (0.74 to 1.86)	**16 more per 1,000** (from 25 fewer to 74 more)	⨁⨁◯◯ Low
Preterm birth											
2	randomised trials	serious[b]	not serious	not serious	not serious	none	80/360 (22.2%)	109/350 (31.1%)	**OR 0.63** (0.45 to 0.89)	**90 fewer per 1,000** (from 142 fewer to 24 fewer)	⨁⨁⨁◯ Moderate
Small for gestational age											
3	randomised trials	serious[b]	not serious	not serious	not serious	none	61/455 (13.4%)	62/445 (13.9%)	**OR 0.96** (0.65 to 1.40)	**5 fewer per 1,000** (from 44 fewer to 45 more)	⨁⨁⨁◯ Moderate
Perinatal mortality											
2	randomised trials	serious[b]	serious[d]	not serious	serious[g]	none	28/362 (7.7%)	28/352 (8.0%)	**OR 0.88** (0.36 to 2.14)	**9 fewer per 1,000** (from 49 fewer to 77 more)	⨁◯◯◯ Very low

CI: confidence interval; **OR:** odds ratio

Explanations

a. Byaruhanga 1997 - 8% of randomised subjects lost to follow-up.
b. Xiang 2020 - No information on concealment of randomisation and intervention allocation. Aspirin dose not specified.
c. Poom 2017 and Moore 2015 - post-hoc secondary analyses.
d. Significant heterogeneity (I2 >40%)
e. Some, but not all, relevant confounders controlled for in all studies
f. Lecarpentier 2013 and Boriboonhirusarn 2017 - aspirin dose not specified
g. Small number of events or wide confidence intervals

CI, confidence interval; *GRADE*, Grading of Recommendations, Assessment, Development and Evaluations; *OR*, odds ratio; *RCT*, randomized controlled trial.

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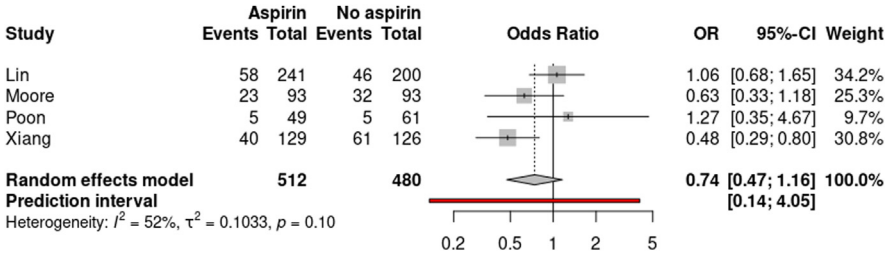
the relationship between low-dose aspirin and the development of superimposed preeclampsia was large, and further high-quality data are required; discussion of the limitations of these analyses is found below.

Similarly, this lack of significant effect persisted even when considering only preterm preeclampsia as the outcome or cases in which aspirin was commenced before 20 weeks' gestation. There was also no significant reduction in the odds of SGA neonates or perinatal mortality. However, there was moderate-quality evidence from 2 RCTs that there was a significant 37% reduction in the odds of preterm birth in the cohort receiving aspirin prophylaxis (OR, 0.63; 95% CI, 0.45−0.89). Unfortunately, the fragility index of 5 is lower than the number of women lost to follow-up in the included studies.

FIGURE 5
Preeclampsia outcome when aspirin initiated before 20 weeks (RCTs)



CI, confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial.

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Comparison with existing literature

Large meta-analyses of pooled data from women with a variety of risk factors for preeclampsia, such as the recent United States Preventive Services Taskforce report[21] and Cochrane review,[39] have found that low-dose aspirin prophylaxis reduces the risk of preeclampsia and other perinatal outcomes. The results of this meta-analysis contradict these

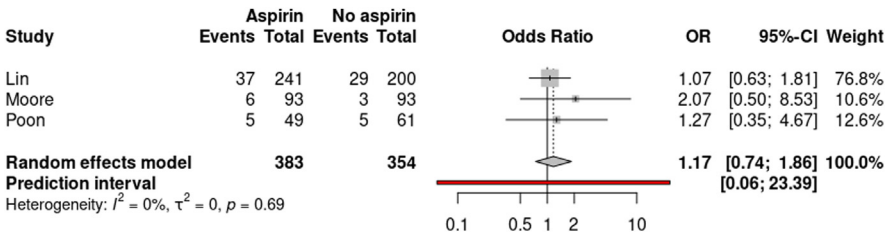
previous reviews. However, our findings are supported by data from women with chronic hypertension: a meta-analysis of individual patient data of high-risk women from the PARIS Collaborative Group found that among women with chronic hypertension (1678 on antiplatelets and 1625 in control group), there was no significant risk reduction for preeclampsia (relative risk [RR], 0.97; 95% CI, 0.84−1.12) following administration of aspirin or dipyridamole, although there was a significant reduction in the RR among the total cohort of women with a variety of risk factors.[19] These differences in results may be explained by the heterogeneity in the populations investigated.

In regard to the timing of aspirin initiation, we found that pooled data from the 5 studies in which aspirin was commenced before 20 weeks' gestation also did not demonstrate a significant reduction in the odds of developing superimposed preeclampsia. This is consistent with previous work that has shown no significant difference in preeclampsia risk between earlier and later initiation among women with risk factors for preeclampsia,[20,21] although there is also evidence to the contrary.[17,18]

Our finding that aspirin prophylaxis significantly reduced the odds of preterm birth is echoed by an individual-participant data meta-analysis of women with risk factors for preeclampsia, which found a significant reduction in risk of preterm birth before 37 weeks' gestation with aspirin and/or dipyridamole (RR, 0.93; 95% CI, 0.86−0.996). Interestingly, when considering only the women with chronic hypertension (1266 on antiplatelets and 1252 in control group), there was a more pronounced effect estimate of a 27% reduction in the risk of spontaneous preterm birth before 37 weeks' gestation (RR, 0.73; 95% CI, 0.53−0.999).[40]

However, this analysis found no significant reduction in preterm birth before 34 weeks or before 28 weeks in women with chronic hypertension, whereas there was a significant reduction in the risk of preterm birth before 34 weeks' gestation for the wider, more diverse cohort (RR, 0.86; 95% CI, 0.76−0.99).[40] These findings suggest that low-dose aspirin prophylaxis may be more efficacious in the prevention of late preterm birth for women with chronic hypertension than for those with other risk factors for preeclampsia, although the test of interaction between treatment group and chronic hypertension history did not indicate significance, and the effect has not been shown for moderate to very preterm birth. Given the hypothesis that placental vascular pathology causes moderate to late preterm birth, and that very preterm birth is associated more with infection and inflammation,[40] it may be theorized that aspirin works well in the prevention of late preterm birth in women with chronic hypertension because of action on placental vascular pathology to which chronic hypertension more greatly predisposes compared with other preeclampsia risk factor groups, although this requires further investigation.

FIGURE 6
Preterm preeclampsia (RCTs)



CI, confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial.

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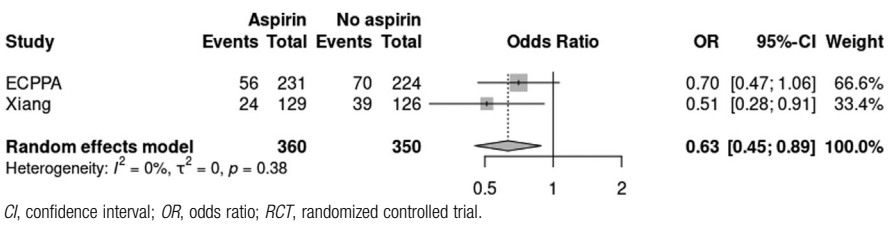
Strengths and limitations

Strengths of this meta-analysis include a large total population size of 2150 pregnant women with chronic hypertension from many different ethnic backgrounds, including subgroup data from the well-known Network of Maternal-Fetal Medicine Units[15] and ASPRE[16] trials. We were able to investigate the relationship between aspirin use, including timing of initiation of aspirin, and a number of different maternal and neonatal outcomes.

The quality of the evidence is notably limited by the observed heterogeneity. This is reflected in the PIs, which suggest that similar future studies may find true effects across a wide range of possibilities, including beneficial but also harmful effects. This heterogeneity may be because of variations in definitions of population (eg, use of different hypertension definitions and whether participants were required to be on treatment for hypertension), exposure (variable aspirin dose, including 3 studies that did not define the dose), and outcomes

FIGURE 7
Preterm birth (RCTs)



CI, confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial.

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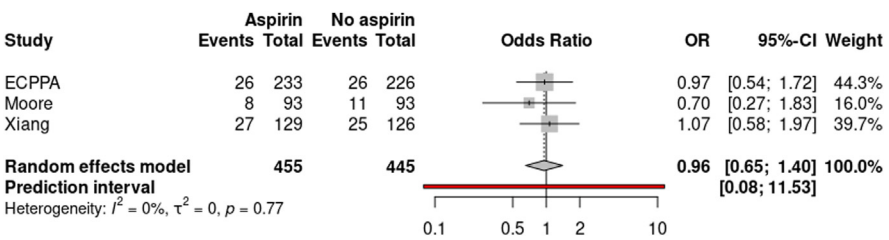
FIGURE 8
Small for gestational age (RCTs)



CI, confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial.

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(such as variations in definitions of superimposed preeclampsia, SGA birth, and preterm gestation). In regard to the main outcome of superimposed preeclampsia, although studies used different definitions, some of which may have underestimated the incidence of superimposed preeclampsia, they all fell within the International Society for the Study of Hypertension in Pregnancy definition[2] described in this review's protocol.[29] The studies were found to have low risk of bias in the measurement of the outcome because there was no evidence that the measurement differed between intervention groups or was influenced by knowledge of intervention status, or that there were systematic errors in measurement of the outcome related to intervention received. Three of the 9 studies (all of which reported on women with a variety of risk factors) described only a definition for preeclampsia, and not one for superimposed preeclampsia in women with chronic hypertension. Future systematic reviews may seek to impose stricter eligibility criteria to limit heterogeneity, and prospective studies including only women with chronic hypertension may improve the identification of superimposed preeclampsia.

Some risk of bias was present in 7 of the 9 studies included. Although these biases did not reach a critical level, there are particular concerns regarding the reported loss to follow-up in multiple RCTs and the relatively low fragility indices, suggesting that those lost to follow-up may have been able to sway the results of the analyses. In addition, there may have been inadequate controlling for confounding factors in the retrospective studies. Furthermore, the use of post hoc secondary analyses of data confers a lack of transparency regarding the selection of reported results, and unspecified dosing of aspirin suggests possible deviation from intervention.

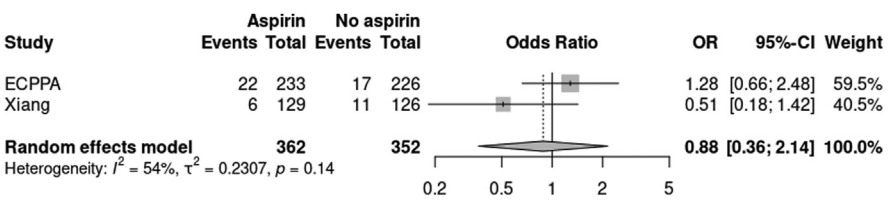
Clinical and research implications

Although low-quality evidence suggests that aspirin had no significant effect on rates of preeclampsia among women with chronic hypertension, moderate-quality evidence suggesting reduction in preterm births has important implications for clinical care. Preterm birth is associated with increased rates of disability and infant death, with higher costs of healthcare both in the neonatal period and in the long term, and important personal consequences for families. The use of aspirin in pregnancies at high risk for preeclampsia has been found to significantly lower rates of preterm birth before 32 weeks, with associated significantly reduced length of neonatal intensive care unit (NICU) stay in the aspirin group (although rates of NICU admission were not affected).[41]

Further research on the value of aspirin in pregnancy is required. Because this is a meta-analysis, we cannot exclude the possibility that there are some beneficial effects that are masked by the heterogeneity and evidence quality issues that we highlighted. Furthermore, because we did not differentiate between provider-initiated and spontaneous preterm birth, we are uncertain about the mechanism of aspirin action in reducing preterm birth. It is worth noting that rates of preterm preeclampsia and SGA were not affected by the use of aspirin, which may suggest that aspirin affects spontaneous preterm birth rather than preterm birth secondary to preterm preeclampsia and SGA.

We have shown that when considering women with chronic hypertension separately from a pooled cohort of women with different risk factors for preeclampsia, aspirin may not be as effective for the prevention of superimposed preeclampsia as previous meta-analyses suggest, but may be more effective for the prevention of late preterm birth in women with chronic hypertension than in other preeclampsia risk factor groups. Given the 25% risk of preeclampsia in women with chronic hypertension[5] and the increasing frequency of cardiovascular disease in pregnancy,[42] a prospective study to investigate the impact of aspirin use for women with chronic hypertension on perinatal and maternal outcomes is

FIGURE 9
Perinatal mortality (RCTs)



CI, confidence interval; *OR*, odds ratio; *RCT*, randomized controlled trial.

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TABLE 3
Summary of meta-analyses of the effect of low-dose aspirin on maternal and neonatal outcomes in women with chronic hypertension

Outcome	Studies (number of patients)	OR (95% CI)	95% PI	Fragility index
Superimposed preeclampsia	6 RCTs (1484)	0.83 (0.55–1.25)	0.27–2.56	11
Superimposed preeclampsia	3 cohort (666)	1.21 (0.78–1.87)	0.07–20.80	NA
Superimposed preeclampsia given early aspirin initiation	4 RCTs (992)	0.74 (0.47–1.16)	0.14–4.05	6
Preterm preeclampsia	3 RCTs (737)	1.17 (0.74–1.86)	0.06–23.39	10
Preterm birth	2 RCTs (710)	0.63 (0.45–0.89)	NA	5
Small for gestational age	3 RCTs (900)	0.96 (0.65–1.40)	0.08–11.53	18
Perinatal mortality	2 RCTs (714)	0.88 (0.36–2.14)	NA	14

CI, confidence interval; *PI*, prediction interval; *NA*, not applicable; *OR*, odds ratio; *RCT*, randomized controlled trial.

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justified and may answer some of the questions raised in this paper.

Conclusions

This meta-analysis was unable to demonstrate a significant change in the odds of superimposed preeclampsia, SGA infants, or perinatal mortality with the use of low-dose aspirin in women with chronic hypertension. However, the significant reduction in preterm birth may confer substantial personal, clinical, and economic benefits, justifying the continued clinical use of aspirin prophylaxis in women with chronic hypertension. Given the mixed quality of the source data and the limitations of the meta-analyses, further work with women with chronic hypertension is required to clarify the value of aspirin prophylaxis. ■

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