The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis

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BACKGROUND: Preeclampsia and fetal growth restriction are major causes of perinatal death and handicap in survivors. Randomized clinical trials have reported that the risk of preeclampsia, severe preeclampsia, and fetal growth restriction can be reduced by the prophylactic use of aspirin in high-risk women, but the appropriate dose of the drug to achieve this objective is not certain.

OBJECTIVE: We sought to estimate the impact of aspirin dosage on the prevention of preeclampsia, severe preeclampsia, and fetal growth restriction.

STUDY DESIGN: We performed a systematic review and meta-analysis of randomized controlled trials comparing the effect of daily aspirin or placebo (or no treatment) during pregnancy. We searched MEDLINE, Embase, Web of Science, and Cochrane Central Register of Controlled Trials up to December 2015, and study bibliographies were reviewed. Authors were contacted to obtain additional data when needed. Relative risks for preeclampsia, severe preeclampsia, and fetal growth restriction were calculated with 95% confidence intervals using random-effect models. Dose-response effect was evaluated using meta-regression and reported as adjusted R^2. Analyses were stratified according to gestational age at initiation of aspirin ($\leq$16 and $>$16 weeks) and repeated after exclusion of studies at high risk of biases.

RESULTS: In all, 45 randomized controlled trials included a total of 20,909 pregnant women randomized to between 50-150 mg of aspirin daily. When aspirin was initiated at $\leq$16 weeks, there was a significant reduction and a dose-response effect for the prevention of preeclampsia (relative risk, 0.57; 95% confidence interval, 0.43—0.75; $P < .001$; R^2, 44%; $P = .036$), severe preeclampsia (relative risk, 0.47; 95% confidence interval, 0.26—0.83; $P = .009$; R^2, 100%; $P = .008$), and fetal growth restriction (relative risk, 0.56; 95% confidence interval, 0.44—0.70; $P < .001$; R^2, 100%; $P = .044$) with higher dosages of aspirin being associated with greater reduction of the 3 outcomes. Similar results were observed after the exclusion of studies at high risk of biases. When aspirin was initiated at $>$16 weeks, there was a smaller reduction of preeclampsia (relative risk, 0.81; 95% confidence interval, 0.66—0.99; $P = .04$) without relationship with aspirin dosage (R^2, 0%; $P = .941$). Aspirin initiated at $>$16 weeks was not associated with a risk reduction or a dose-response effect for severe preeclampsia (relative risk, 0.85; 95% confidence interval, 0.64—1.14; $P = .28$; R^2, 0%; $P = .838$) and fetal growth restriction (relative risk, 0.95; 95% confidence interval, 0.86—1.05; $P = .34$; R^2, not available; $P = .563$).

CONCLUSION: Prevention of preeclampsia and fetal growth restriction using aspirin in early pregnancy is associated with a dose-response effect. Low-dose aspirin initiated at $>$16 weeks' gestation has a modest or no impact on the risk of preeclampsia, severe preeclampsia, and fetal growth restriction. Women at high risk for those outcomes should be identified in early pregnancy.

Key words: aspirin, fetal growth restriction, meta-analysis, meta-regression, preeclampsia, pregnancy, systematic review

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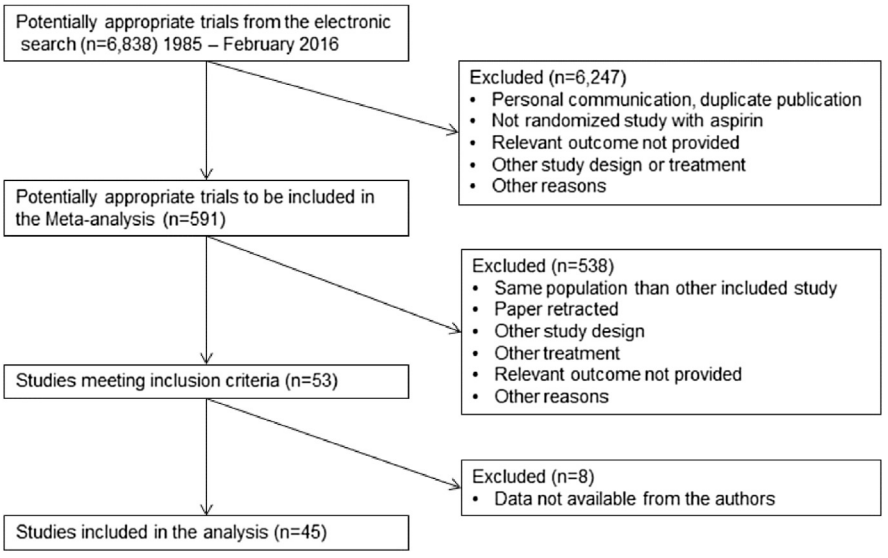
Introduction

Preeclampsia (PE) and fetal growth restriction (FGR) are important causes of perinatal death and handicap in survivors. PE is responsible for >70,000 maternal deaths each year around the world.[1] Additionally, PE is associated with increased long-term risk for development of cardiovascular disease in both the mother and her infant.[2-4]

Several studies examined the possibility that prophylactic use of low-dose aspirin in women at high risk of developing PE could reduce the prevalence of the disease. Meta-analyses of randomized controlled trials (RCTs) of aspirin vs placebo or no treatment showed that the prevalence of PE and FGR can be reduced by aspirin started at ≤16 weeks' gestation and the effect is most marked for severe PE leading to delivery at <34 weeks' gestation; aspirin started at >16 weeks had no significant effect on the prevalence of severe PE or FGR.[5,6]

FIGURE 1
Study selection process



Selection tree for selection of included articles.

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TABLE 1
Characteristics of included studies according to gestational age at initiation of intervention

Study	N	Inclusion criteria	Intervention		
≤16 wk			Aspirin	Controls	Onset, wk
Tulppala et al,[63] 1997	66	Previous consecutive miscarriage	50 mg	Placebo	<7
Benigni et al,[32] 1989	33	History risk factors[a]	60 mg	Placebo	12
[b]Caritis et al,[34] 1998	652	History risk factor[a]	60 mg	Placebo	13–16
[b]Sibai et al,[60] 1993	644	Nulliparity	60 mg	Placebo	13–16
[b]Golding,[41] 1998	1997	Nulliparity	60 mg	Placebo	12–16
[b]Ebrashy et al,[38] 2005	136	Abnormal uterine artery Doppler plus history risk factors[a]	75 mg	No treatment	14–16
Zhao et al,[69] 2012	237	History risk factor[a]	75 mg	Placebo	13–16
Odibo et al,[54] 2015	30	History risk factor[a]	80 mg	Placebo	11–13
Porreco et al,[56] 1993	90	Nulliparity + multiple gestation	80 mg	Placebo	<16
Jamal et al,[46] 2012	70	Diagnose PCOS before pregnancy, 18–40 y, singleton, no history of diabetes or HTN	80 mg	No treatment	6–12
Mesdaghinia et al,[50] 2011	80	Abnormal uterine artery Doppler	80 mg	No treatment	12–16
August et al,[26] 1994	54	History risk factors[a]	100 mg	Placebo	13–15
Azar and Turpin,[28] 1990	91	History risk factors[a]	100 mg[c]	No treatment	16
Bakhti and Vaiman,[29] 2011	84	Nulliparity	100 mg	No treatment	8–10
Chiaffarino et al,[35] 2004	35	Chronic HTN with or without history risk factors[a]	100 mg	No treatment	<14
Dasari et al,[36] 1998	50	Nulliparity	100 mg	Placebo	12
Hermida et al,[45] 1997	107	History risk factors[a]	100 mg	Placebo	12–16

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017. *(continued)*

TABLE 1
Characteristics of included studies according to gestational age at initiation of intervention *(continued)*

Study	N	Inclusion criteria	Intervention		
Ayala et al,[27] 2013	350	History risk factors[a]	100 mg	Placebo	12–16
Michael et al,[51] 1992	110	HTN with history risk factors[a]	100 mg	Placebo	<16
[b]Villa et al,[64] 2013	121	Abnormal uterine artery Doppler and history risk factors[a]	100 mg	Placebo	13–14
Beaufils et al,[31] 1985	93	History risk factors[a]	150 mg[c]	No treatment	14
>16 wk					
Zimmermann et al,[70] 1997	26	Abnormal uterine artery Doppler	50 mg	No treatment	22–24
[b]Caritis et al,[34] 1998	1851	History risk factor[a]	60 mg	Placebo	17–26
CLASP,[24] 1994	2492	History risk factors[a]	60 mg	Placebo	20–32
ECPPA,[25] 1996	606	History risk factors[a]	60 mg	Placebo	20–32
Ferrier et al,[39] 1996	43	Nulliparity with abnormal umbilical artery Doppler	60 mg	Placebo	22–24
[b]Golding,[41] 1998	4292	Nulliparity	60 mg	Placebo	20–32
Hauth et al,[43]1993	606	Nulliparity	60 mg	Placebo	24
[b]Sibai et al,[60] 1993	2340	Nulliparity	60 mg	Placebo	17–25
Kim et al,[47] 1997	70	History risk factors[a]	60 mg	No treatment	20–24
Wallenburg et al,[66] 1986	46	Nulliparity with positive angiotensin II sensitivity test	60 mg	Placebo	28
Wallenburg et al,[65] 1991	36	Nulliparity with positive angiotensin II sensitivity test	60 mg	Placebo	28–34
Byaruhanga et al,[33] 1998	230	History of PE, or chronic HTN	75 mg	Placebo	20–28
Davies et al,[37] 1995	118	Nulliparity	75 mg	Placebo	18
McParland et al,[49] 1990	100	Nulliparity with abnormal uterine artery Doppler	75 mg	Placebo	24
Rotchell et al,[57] 1998	1485	All pregnant women	75 mg	Placebo	20–32
Wang and Li,[67] 1996	84	History risk factors[a]	75 mg	Placebo	28–34
Rogers 1999[106]	193	Normotensive, primigravid with MAP ≥80 mm Hg and <106 mm Hg early in second trimester and MAP >60 mm Hg	80 mg	Unclear	22
Schrocksnadel et al,[59] 1992	41	Nulliparity with positive roll-over test	80 mg	Placebo	28–32
Grab et al,[42] 2000	43	Singleton with history risk factor	100 mg	Placebo	20
Omrani et al,[55] 1992	40	History risk factors[a] with positive roll-over test	100 mg	Placebo	28–30
Gallery et al,[40] 1997	120	History risk factors[a]	100 mg	Placebo	17–19
McCowan et al,[48] 1999	99	FGR with abnormal umbilical artery Doppler	100 mg	Placebo	24–36
Morris et al,[52] 1996	102	Nulliparity with abnormal umbilical artery Doppler	100 mg	Placebo	17–19
Newnham et al,[53] 1995	51	IUGR and abnormal umbilical artery Doppler	100 mg	Placebo	28–36
Schiff et al,[58] 1989	65	History risk factors[a] with positive roll-over test	100 mg	Placebo	28–29
Trudinger et al,[62] 1988	46	Abnormal umbilical artery Doppler	150 mg	Placebo	28–36
Yu et al,[68] 2003	554	Abnormal uterine artery Doppler	150 mg	Placebo	22–24

FGR, fetal growth restriction; *HTN*, hypertension; *IUGR*, intrauterine growth restriction; *MAP*, mean arterial pressure; *PCOS*, polycystic ovary syndrome; *PE*, preeclampsia.

[a] Includes history of chronic HTN, cardiovascular or endocrine disease, pregnancy HTN, or fetal growth restriction; [b] Studies provided additional information on request; [c] With dipyridamole 150–300 mg daily.

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Consequently, several national societies are now recommending that women identified as being at high risk for PE should receive low-dose aspirin starting from <16 weeks' gestation.[7-10] The recommended dose of aspirin varies between 60-150 mg daily but the optimal dose remains unclear. Observational studies suggested that 60-80 mg could be insufficient in some women and that 100-160 mg may be necessary to optimize prevention of PE.[11-14]

The objective of this study is to evaluate the dose-response effect of aspirin for the prevention of PE and FGR.

Materials and Methods

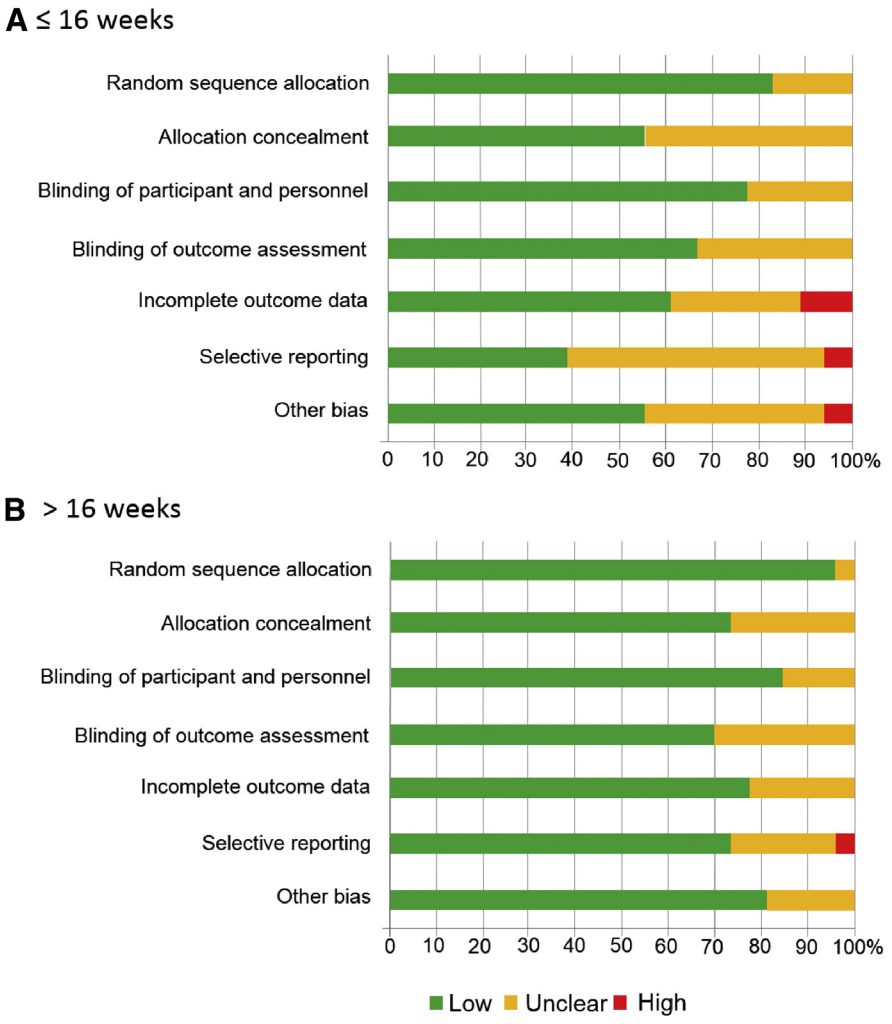
We performed a systematic review and meta-analysis of RCTs that evaluated the impact of aspirin during pregnancy. Relevant trials were identified through a search of Embase, MEDLINE, the Cochrane Central Register of Controlled Trials, and the Web of Science databases including studies reported from January 1985 through December 2015. We used a combination of key words and Medical Subject Headings terms: "aspirin," "antiplatelet," "acetylsalicylic acid," "ASA," "pregnancy-complication," "pregnancy," "preeclampsia," "pre-eclampsia," "hypertension," "blood pressure," "eclampsia," "PIH," and "toxemia." No language restriction was imposed. A first reviewer selected all the citations requiring a detailed evaluation. Two independent reviewers selected relevant abstracts and citations for complete evaluation. References of other systematic reviews were also searched for additional studies. In case of missing data in a relevant article, the corresponding and/or the primary authors were contacted for additional information (outcomes and data stratified according to gestational age at randomization). The quality of this review was validated with the preferred reporting items for systematic reviews and meta-analyses tool.[15]

Trials involving pregnant women randomized to either aspirin with or without dipyridamole or to placebo or no treatment were included. Studies using other treatment, other study design, using the same population, or in which relevant data could not be extracted were excluded. Studies were stratified by gestational age at entry based on previous publications (≤16 vs >16 weeks' gestation). The quality of studies was evaluated using the Cochrane handbook criteria for judging risk of bias and a sensitivity analysis was performed to evaluate the effect excluding: (1) studies at high risk of bias; (2) studies with low risk of PE (<7% prevalence in control group); and (3) excluding studies using dipyridamole.[16-18]

Outcomes of interest included PE, usually defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg that occurs >20 weeks' gestation in combination with proteinuria, defined as urinary excretion ≥300 mg protein in a 24-hour urine specimen or ≥1+ protein on dipstick.[19] Secondary outcomes included severe PE (any definition) and FGR, defined as birthweight <10th or <5th percentile for gestational age or similar definition.

Relative risks (RR) were calculated for each study and pooled for global analysis using DerSimonnian and Laird random effect to take into account variability and heterogeneity between studies. Heterogeneity between studies was calculated using Higgins I^2 and considered high if ≥50%.[20,21] Random-effects meta-regression, weighted by the size of the studies, was performed to evaluate the dose-response effect of aspirin. An adjusted R^2 (considering the degree of freedom) coefficient and its *P* value were reported for each outcome. The adjusted R^2 represents the proportion of the variance in the dependent variable (in this case, the RR of the disease) that is predictable from the independent variable (dose of aspirin). An adjusted R^2 of 0% or a negative value (reported as 0%) indicates that the variance around the mean cannot be explained by the aspirin

FIGURE 2
Assessment of risk of bias in studies included following Cochrane handbook



Aspirin initiated **A,** ≤16 weeks and **B,** >16 weeks of gestation.

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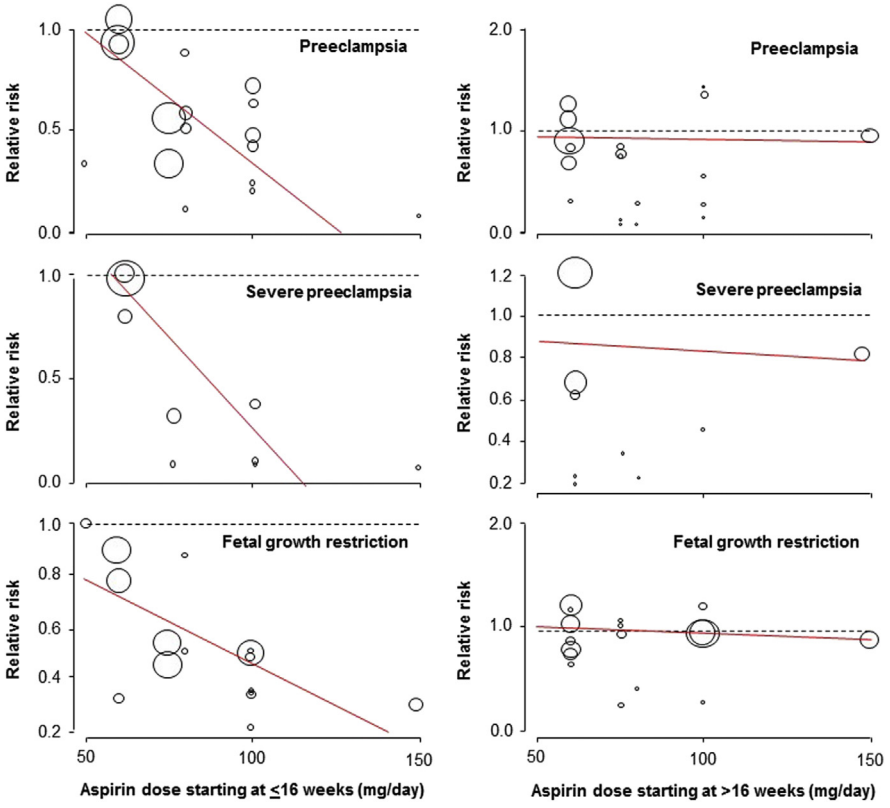
FIGURE 3
Evaluation of aspirin's dose-response effect when initiated at or before 16 weeks or after 16 weeks of gestation



Bubble plots with fitted meta-regression line that report relationship between aspirin dosage and relative risks for each adverse pregnancy, according to gestational age at initiation of aspirin.

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dose, while an adjusted R^2 of 100% indicates that the dose of aspirin could explain the entire variability between the studies.[22] Publication bias was evaluated using funnel plots and symmetry using Egger test, for which a P value $<.1$ was considered asymmetrical.[23]

Statistical analysis was performed using Review Manager 5.0.25 software (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark), Stata release 14.0 (StataCorp, College Station, TX), and SAS 9.2 software (SAS Institute Inc, Cary, NC).

Results

The literature search identified 6838 potential citations including 53 studies that met the inclusion criteria. Data stratified according to gestational age were available for 45 studies that enrolled 20,909 participants (Figure 1).[24-70] The characteristics of each study are reported in Table 1.

Aspirin initiated at ≤16 weeks' gestation

Data for 5130 participants randomized at ≤16 weeks' gestation were available from 21 studies. The dose of aspirin varied between 50-150 mg daily, including 2 studies that combined 300 mg of dipyridamole with aspirin. In 7 RCTs, a placebo was not used and participants allocated to the control group received no treatment. The risk of bias tool described most studies as being at low or unclear risk of bias (Figure 2, A).

Aspirin was associated with a significant reduction in the prevalence of PE, severe PE, and FGR with a significant dose-response relationship (Figure 3, Table 2, Supplemental Figures 1, 2, and 3). As a secondary analysis, we compared the 2 most studied dosages (60 mg daily: 4 RCTs, n = 3326; and 100 mg daily: 7 RCTs, n = 985); aspirin 100 mg vs 60 mg was significantly more effective in reduction of PE (RR, 0.48; 95% confidence interval [CI], 0.31−0.74 vs RR, 0.93; 95% CI, 0.75−1.15; $P<.001$); severe PE (RR, 0.24; 95% CI, 0.09−0.65 vs RR, 0.96; 95% CI, 0.71−1.28; $P=.002$), and FGR (RR, 0.45; 95% CI, 0.28−0.71 vs RR, 0.78; 95% CI, 0.53−1.16; $P=.006$).

Sensitivity analysis revealed a similar dose-response relationship of aspirin initiated at ≤16 weeks for the prevention of PE in high-quality studies (15 studies, R^2, 100%; $P=.004$), but the association was marginally significant in the subgroup of studies that did not used dipyridamole (16 studies, R^2, 41%; $P=.06$) and in the subgroup of studies that included high-risk populations (defined as a rate of PE >7% in the control group; 17 studies, R^2, 36%; $P=.06$). The number of studies that randomized women at low risk of PE was too low to evaluate the dose-response effect.

Aspirin initiated at >16 weeks' gestation

Data for 15,779 participants randomized at >16 weeks' gestation were available from 27 studies. The dose of aspirin varied between 50-150 mg daily. In 2 RCTs, a placebo was not used and participants allocated to the control group received no treatment. The risk of bias tool described most studies as being at low or unclear risk of bias (Figure 2, B).

Aspirin started at >16 weeks was associated with a significant reduction in the prevalence of PE, but there was no dose-response relationship and there was no significant effect on the prevalence of severe PE or FGR (Table 3, Supplemental Figures 4, 5, and 6).

Analysis of the funnel plots suggest the possibility of publication bias because small studies with no beneficial effect were missing (Figure 4).[71] Moreover Egger test suggest asymmetry of the funnel plots: aspirin ≤16

TABLE 2
Perinatal outcomes ≤16 weeks according to dose of aspirin at initiation of intervention

Outcome ≤16 wk	No. of trials	No. of participants	Relative risk (95% confidence interval) random effect	*P* value	I^2	Dose-response correlation	
						Adjusted R^2	*P* value
Preeclampsia							
50 mg	1	66	0.33 (0.04–3.04)	.33	n/a	44%	.036
60 mg	4	3326	0.93 (0.75–1.15)	.49	0%		
75 mg	2	373	0.42 (0.25–0.70)	.001	72%		
80 mg	4	270	0.52 (0.26–1.01)	.06	1%		
100 mg	7	985	0.48 (0.31–0.74)	.0009	0%		
150 mg	1	93	0.07 (0.00–1.25)	.07	n/a		
Total	19	5113	0.57 (0.43–0.75)	<.001	52%		
Severe preeclampsia							
60 mg	3	3279	0.96 (0.71–1.28)	.77	0%	100%	.008
75 mg	2	373	0.24 (0.09–0.65)	.005	9%		
100 mg	3	334	0.23 (0.08–0.64)	.005	0%		
150 mg	1	93	0.07 (0.00–1.25)	.07	n/a		
Total	9	4079	0.47 (0.26–0.83)	.009	60%		
Fetal growth restriction							
50 mg	1	46	1.00 (0.22–4.45)	1.00	n/a	100%	.044
60 mg	3	1378	0.78 (0.53–1.16)	.22	0%		
75 mg	2	373	0.48 (0.32–0.72)	.0004	0%		
80 mg	3	180	0.64 (0.11–3.74)	.62	0%		
100 mg	7	869	0.45 (0.28–0.71)	.0007	0%		
150 mg	1	93	0.29 (0.10–0.82)	.02	n/a		
Total	17	2939	0.56 (0.44–0.70)	<.001	0%		

n/a, not applicable.

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weeks: *P* value = .091; aspirin >16 weeks: *P* value = .007.

Comment

Main findings

This meta-analysis demonstrates that the beneficial effect of prophylactic aspirin for the prevention of PE, severe PE, and FGR is conditional on the onset of treatment being at ≤16 weeks' gestation and has a dose-response effect. The actual evidence shows that 60 mg of aspirin initiated at any time during pregnancy has no impact on the risk of PE, severe PE, and FGR.

The exact mechanism by which aspirin acts to prevent PE and FGR remains unclear. However, the finding that therapy is effective only when treatment is initiated at ≤16 weeks is compatible with the knowledge that certainly severe PE, preterm PE, and FGR are associated with impaired placentation; in normal pregnancies the physiological transformation of uterine spiral arteries is completed by 16-18 weeks' gestation.[72-76] We hypothesized that aspirin started ≤16 weeks can reduce deep placentation disorders in women at high risk of poor placentation and therefore reduce the early and severe forms of PE as well as FGR. However, few studies evaluated the impact of aspirin initiated in early pregnancy on placentation. On the other hand, term and mild PE are likely to be the consequences of other pathologic processes that can also lead to the maternal syndrome.[77,78] The optimal approaches for the prediction and prevention of the preterm and severe forms of PE are likely to be different than those for the term and mild forms of the disease. As for the need of a minimum dose of aspirin, previous observational studies reported that in a high proportion of women a dose of <100 mg/d is not sufficient to affect platelet function or reduce PE.[11-14]

The clinical impact of such finding is important because maternal history and characteristics, maternal nutritional status, as well as several ultrasound and biochemical markers can identify women who will develop PE, severe PE,

TABLE 3
Perinatal outcomes >16 weeks according to dose of aspirin at initiation of intervention

Outcome >16 wk	No. of trials	No. of participants	Relative risk (95% confidence interval) random effect	*P* value	I^2	Dose response	
						Adjusted R^2	*P* value
Preeclampsia							
50 mg	1	26	2.00 (0.44–9.08)	.37	n/a	0%	.941
60 mg	8	12,274	0.88 (0.68–1.12)	.30	57%		
75 mg	4	1933	0.69 (0.42–1.15)	.16	20%		
80 mg	2	234	0.21 (0.06–0.70)	.01	0%		
100 mg	5	349	0.61 (0.26–1.44)	.26	52%		
150 mg	1	554	0.95 (0.67–1.35)	.77	n/a		
Total	21	15,370	0.81 (0.66–0.99)	.04	48%		
Severe preeclampsia							
60 mg	6	9358	0.87 (0.60–1.25)	.45	58%	0%	.838
75 mg	1	118	0.34 (0.01–8.29)	.51	n/a		
80 mg	1	41	0.17 (0.01–3.41)	.25	n/a		
100 mg	1	65	0.46 (0.04–4.78)	.51	n/a		
150 mg	1	554	0.82 (0.44–1.51)	.52	n/a		
Total	10	10,136	0.85 (0.64–1.14)	.28	37%		
Fetal growth restriction							
50 mg	1	26	2.00 (0.21–19.44)	.55	n/a	n/a	.563
60 mg	7	7438	0.96 (0.78–1.17)	.67	13%		
75 mg	4	538	0.82 (0.49–1.38)	.46	26%		
80 mg	1	41	0.43 (0.04–4.40)	.48	n/a		
100 mg	4	325	0.96 (0.84–1.11)	.59	0%		
150 mg	1	554	0.90 (0.67–1.22)	.51	n/a		
Total	18	8922	0.95 (0.86–1.05)	.34	0%		

n/a, not applicable because there were not enough permutations for this statistical comparison.

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early-onset PE, and FGR before the first symptoms, and as early as the first trimester of pregnancy.[79-96] Combined screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor in the first trimester has been associated with a detection rate of 75% of preterm PE and 47% of PE at a false-positive rate of 10%.[97] This growing body of evidences suggests that preterm PE and FGR can be predicted in early pregnancy and prevented with a minimum dose of aspirin initiated also in early pregnancy.[98,99] The Aspirin for Evidence-Based Preeclampsia Prevention Trial is evaluating the impact of aspirin at 150 mg daily started at the end of the first trimester for the prevention of preterm PE in women identified at high risk of preterm PE using such combined screening.[100]

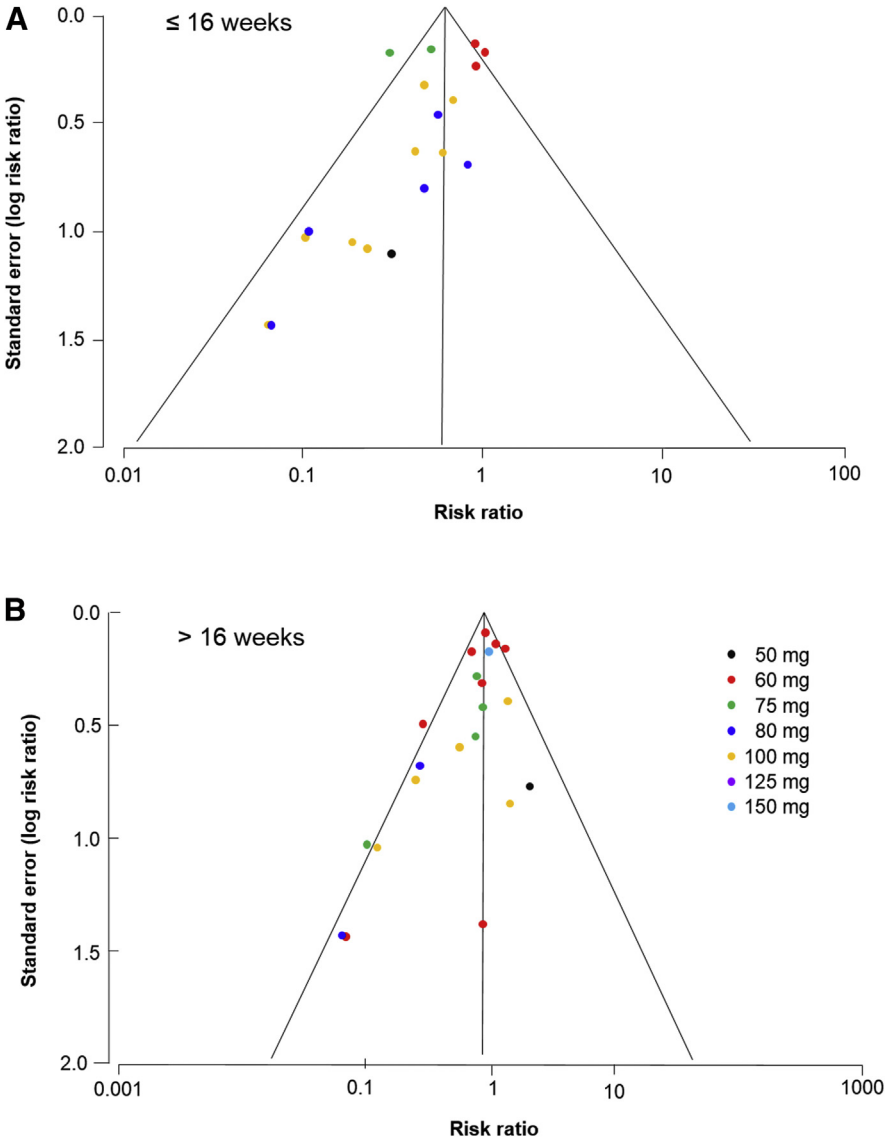
Comparison with previous studies

The finding that low-dose aspirin started at ≤16 weeks in high-risk women reduces the prevalence of PE and FGR is in agreement with that of previous meta-analyses.[5,6,101,102] Similarly, the finding that the effectiveness of aspirin is not only dependent on the gestational age at initiation of treatment but also on the dose of the drug is supported by the results of a previous meta-analysis, from the Cochrane Database, which reported a greater reduction in the risk of PE with the use of aspirin >75 mg/d (17 trials; N = 3061; RR, 0.64; 95% CI, 0.51–0.80) or the combination of aspirin >75 mg/d and dipyridamole (5 trials; N = 506; RR, 0.30; 95% CI, 0.15–0.60) compared to aspirin ≤75 mg/d (21 trials; N = 26,984; RR, 0.88; 95% CI, 0.81–0.95).[103] Another meta-analysis (13 trials; N = 13,234) reported that the effect of aspirin for the prevention of FGR was greater when treatment started at ≤16 weeks' gestation and the dose was 100-150 mg/d rather than 50-80 mg/d.[104]

Limitations

The main limitation of this meta-analysis is the absence of large RCTs that recruited all participants in early

FIGURE 4
Funnel plot of trials for preeclampsia



Aspirin initiated **A,** ≤16 weeks and **B,** >16 weeks of gestation.

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pregnancy and more specifically ≤16 weeks of gestation. Most data from participants recruited at ≤16 weeks' gestation come from small to moderate RCTs or from subgroups of participants recruited in larger RCTs. It could be argued that the use of subgroups (several dosages, several gestational ages) and multiple analyses could lead to potential biases.[105] An additional limitation is that we are unable to determine the optimal dose of aspirin based on this meta-regression analysis, as the number of participants per subgroups is too small, and there is unexplained heterogeneity in some subgroup. Two dosages (60 and 100 mg/d) were studied in sufficient depth to allow direct comparison. Data from large, high-quality trials show that 60 mg/d has no significant impact on the prevalence of PE, severe PE, or FGR. In contrast, all of these outcomes were associated with a significant reduction in prevalence when 100 mg/d was started at ≤16 weeks' gestation.

Conclusions

The results of this meta-analysis suggest that in high-risk women the effect of aspirin for the prevention of PE, severe PE, and FGR is dose-dependent and optimal when initiated ≤16 weeks of gestation. ■

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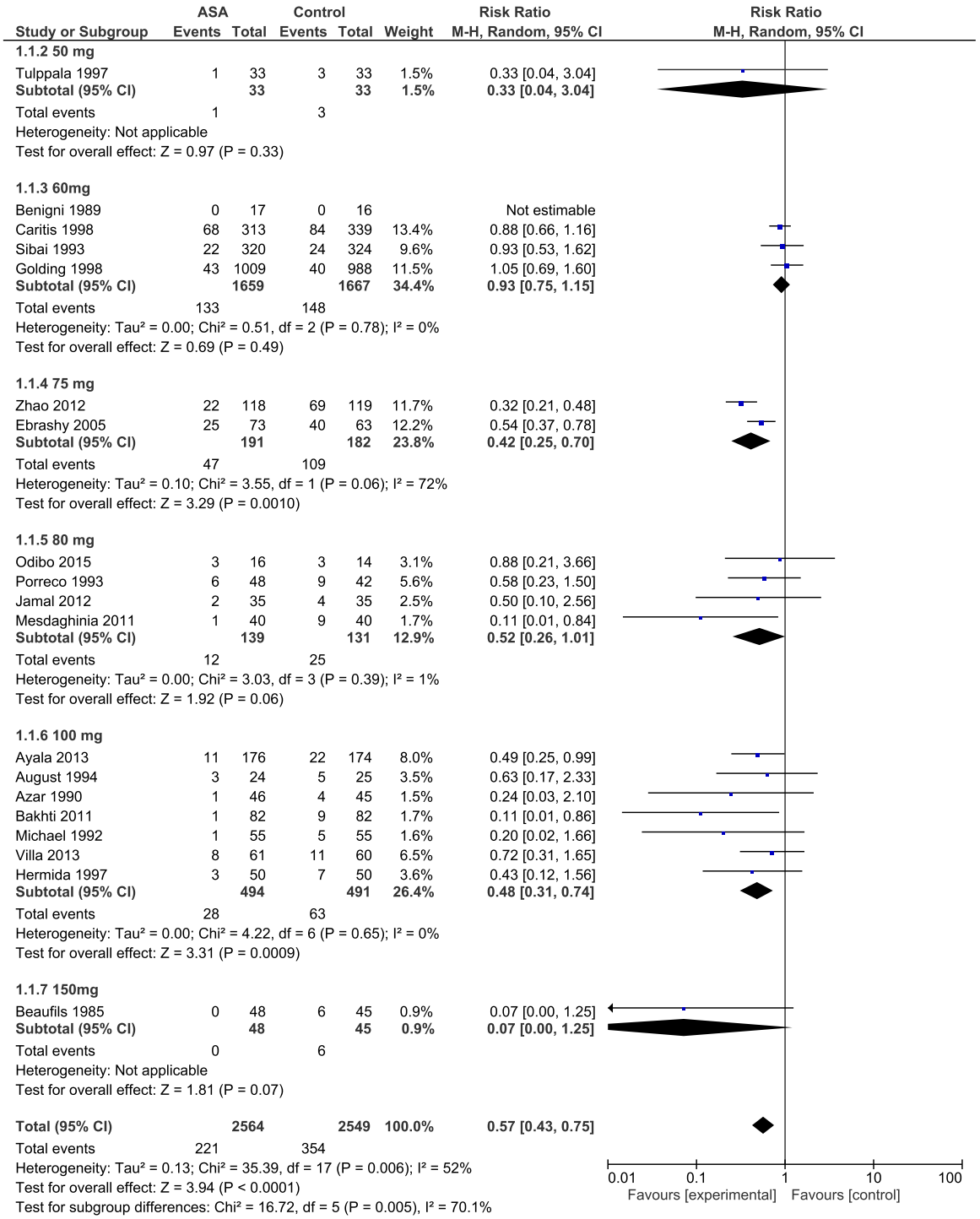
SUPPLEMENTAL FIGURE 1

Forest plot of effect of low-dose aspirin on risk of preeclampsia 16 weeks, subgrouped by aspirin dose

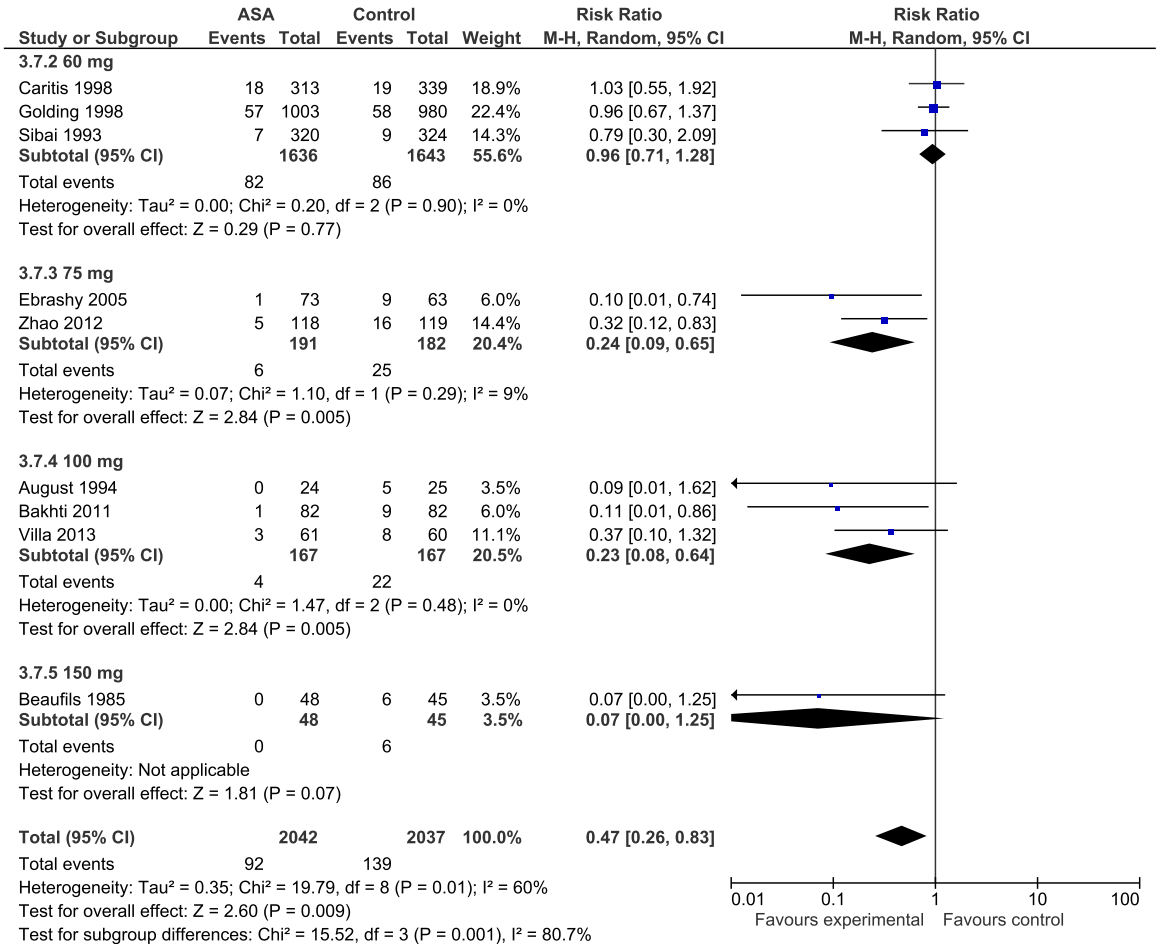


CI, confidence interval; *M-H*, Mantel-Haenszel.

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.

SUPPLEMENTAL FIGURE 2

Forest plot of effect of low-dose aspirin on risk of severe preeclampsia 16 weeks, subgrouped by aspirin dose

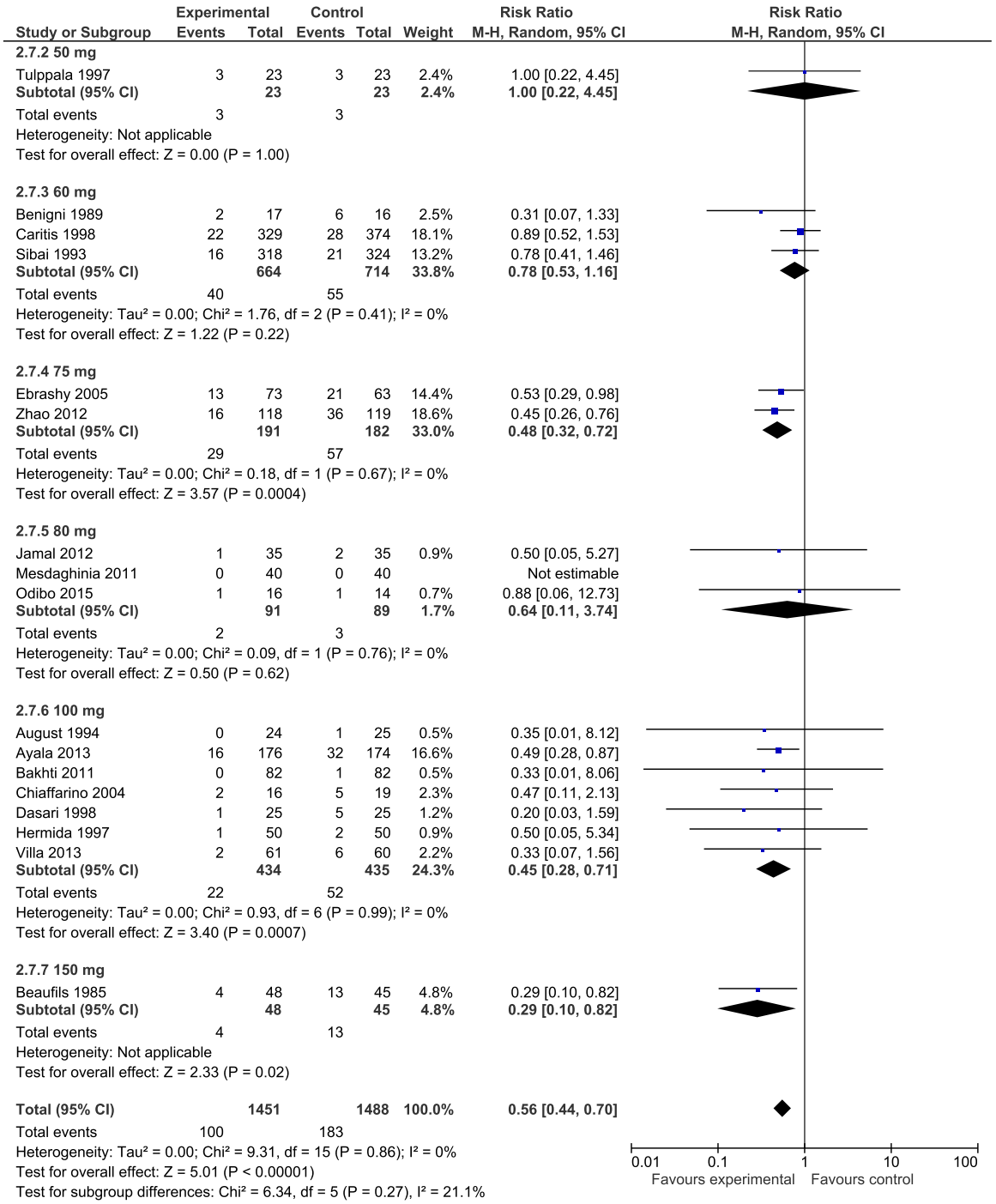


CI, confidence interval; *M-H*, Mantel-Haenszel.

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.

SUPPLEMENTAL FIGURE 3

Forest plot of effect of low-dose aspirin on risk of fetal growth restriction 16 weeks, subgrouped by aspirin dose

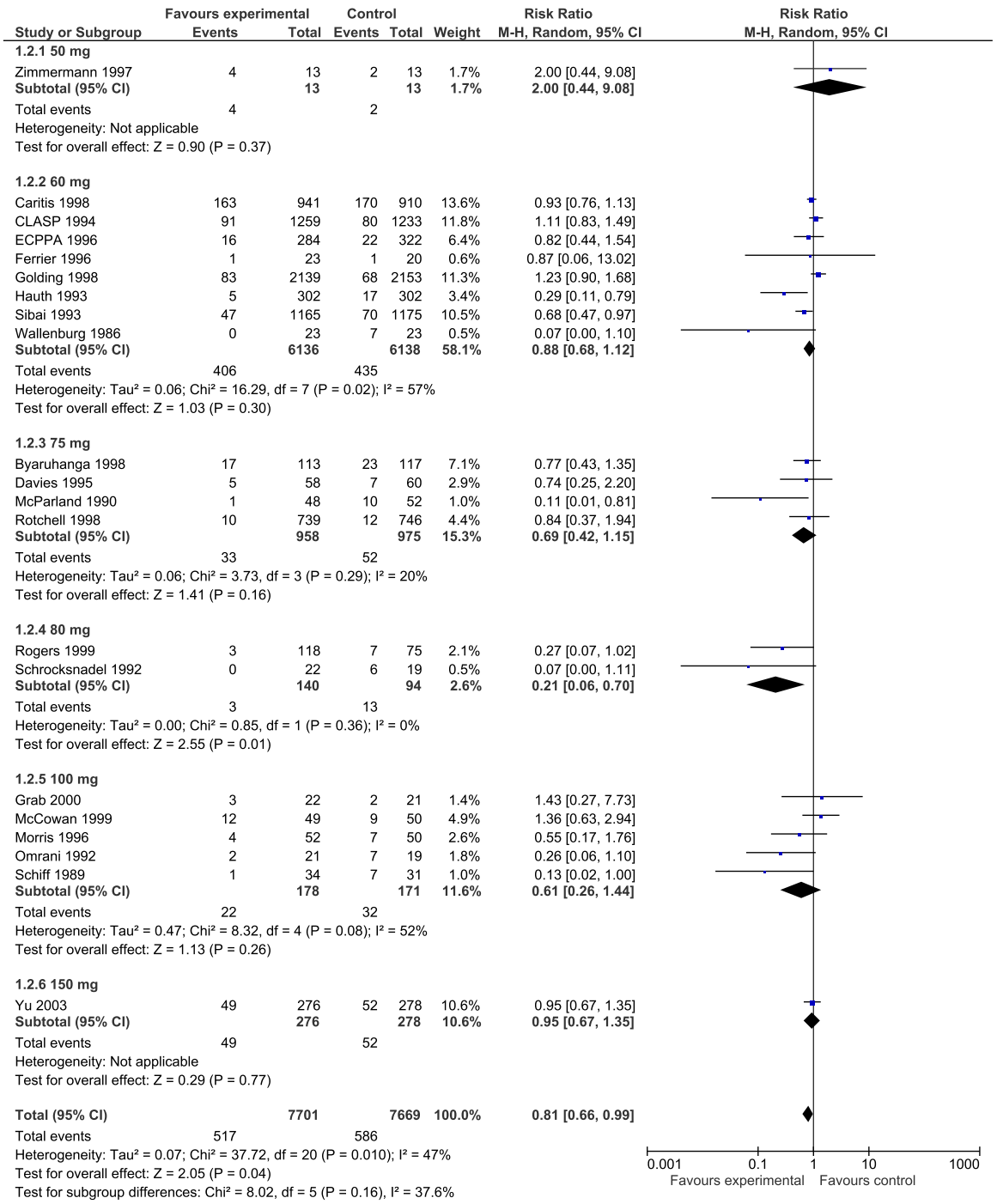


CI, confidence interval; *M-H*, Mantel-Haenszel.

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.

SUPPLEMENTAL FIGURE 4

Forest plot of effect of low-dose aspirin on risk of preeclampsia >16 weeks, subgrouped by aspirin dose

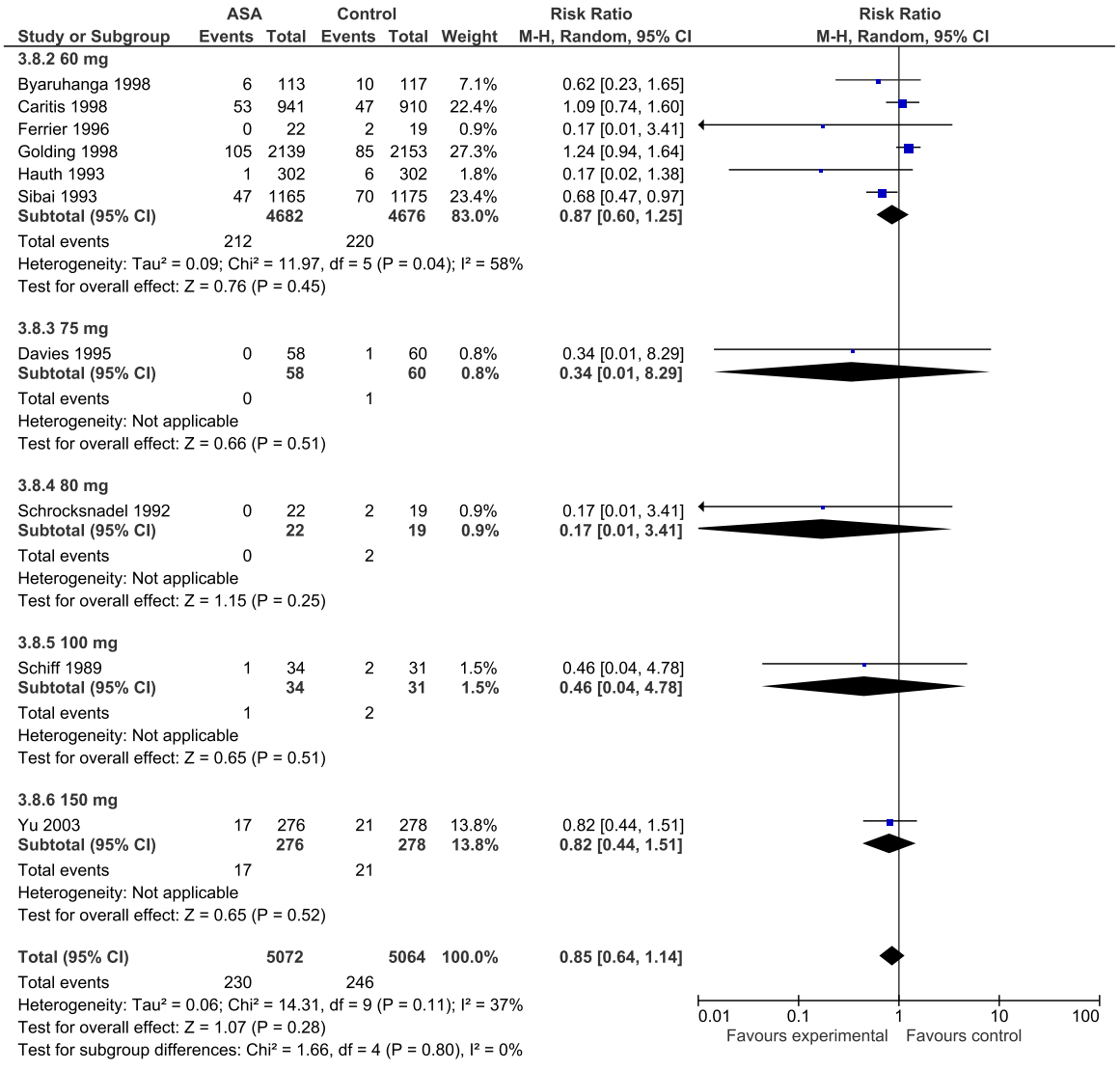


CI, confidence interval; *M-H*, Mantel-Haenszel.

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.

SUPPLEMENTAL FIGURE 5

Forest plot of effect of low-dose aspirin on risk of severe preeclampsia >16 weeks, subgrouped by aspirin dose

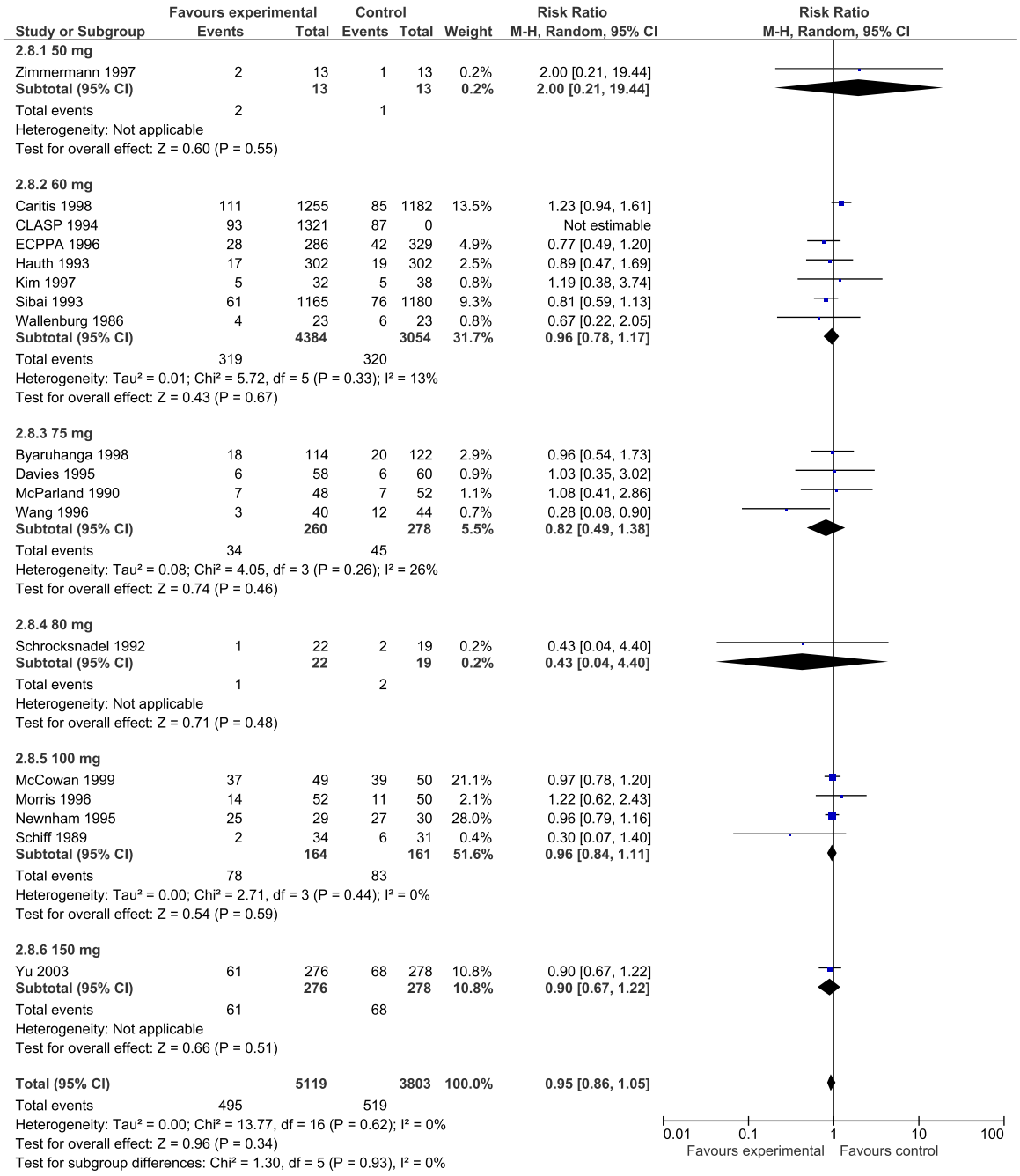


CI, confidence interval; *M-H*, Mantel-Haenszel.

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.

SUPPLEMENTAL FIGURE 6

Forest plot of effect of low-dose aspirin on risk of fetal growth restriction >16 weeks, subgrouped by aspirin dose



CI, confidence interval; *M-H*, Mantel-Haenszel.

Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.