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SYSTEMATIC REVIEW

Calcium for pre-eclampsia prevention: A systematic review and network meta-analysis to guide personalised antenatal care

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Abstract

Background: Calcium supplementation reduces the risk of pre-eclampsia, but questions remain about the dosage to prescribe and who would benefit most.

Objectives: To evaluate the effectiveness of high (≥1 g/day) and low (<1 g/day) calcium dosing for pre-eclampsia prevention, according to baseline dietary calcium, pre-eclampsia risk and co-interventions, and intervention timing.

Search strategy: CENTRAL, PubMed, Global Index Medicus and CINAHL, from inception to 2 February 2021, clinical trial registries, reference lists and expert input (CRD42018111239).

Selection criteria: Randomised controlled trials of calcium supplementation for pre-eclampsia prevention, for women before or during pregnancy. Network meta-analysis (NMA) also included trials of different calcium doses.

Data collection and analysis: Two independent reviewers extracted published data. The meta-analysis employed random-effects models and the NMA, a Bayesian random-effects model, to obtain direct and indirect effect estimates.

Main results: The meta-analysis included 30 trials ($N = 20\,445$ women), and the NMA to evaluate calcium dosage included 25 trials ($N = 15\,038$). Calcium supplementation prevented pre-eclampsia similarly with a high dose (RR 0.49, 95% CI 0.36–0.66) or a low dose (RR 0.49, 95% CI 0.36–0.65). By NMA, high-dose (vs low-dose) calcium did not differ in effect (RR 0.79, 95% CI 0.43–1.40). Calcium was similarly effective regardless of baseline pre-eclampsia risk, vitamin D co-administration or timing of calcium initiation, but calcium was ineffective among women with adequate average baseline calcium intake.

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Conclusions: Low- and high-dose calcium supplementation are effective for pre-eclampsia prevention in women with low calcium intake. This has implications for population-level implementation where dietary calcium is low, and targeted implementation where average intake is adequate.

Tweetable abstract: A network meta-analysis of 25 trials found that low-dose calcium supplementation (<1 g/day) is as effective as high-dose calcium supplementation (≥1 g/day) in halving the risk of pre-eclampsia when baseline calcium intake is low.

KEYWORDS
calcium, meta-analysis, network meta-analysis, pre-eclampsia, prevention, randomised controlled trials

1 | INTRODUCTION

Complicating between 2% and 5% of pregnancies worldwide, pre-eclampsia is characterised by new-onset hypertension and maternal, fetal or placental manifestations after 20 weeks of gestation.[1] The global impact of pre-eclampsia is substantial, being associated with approximately 30 000 maternal and >500 000 perinatal deaths annually, of which >99% occur in low- and middle-income countries (LMICs).[2,3] Moreover, pre-eclampsia is associated with an excess global burden of maternal near-miss events, fetal growth restriction, preterm birth and neonatal morbidity.[4] In women identified at high risk for developing pre-eclampsia by multivariable assessment at 11^{+0}–13^{+6} weeks of gestation, aspirin (150 mg/day) prevents 60% of preterm pre-eclampsia, without affecting the incidence of term disease (≥37^{+0} weeks of gestation),[5] which represents at least 70% of pre-eclampsia cases.[6]

Systematic reviews have identified that calcium supplementation during pregnancy reduces the risk of developing pre-eclampsia (RR 0.45, 95% CI 0.31–0.65), as well as serious maternal morbidity and preterm birth.[7,8] The World Health Organization (WHO) strongly recommends 1.5–2.0 g elemental calcium daily from 20^{+0} weeks of gestation for pregnant women with low dietary calcium intake.[9] However, there are outstanding questions about who should receive calcium for pre-eclampsia prevention (based on the adequacy of baseline calcium intake or baseline pre-eclampsia risk), and how that calcium should be administered (i.e. the minimal dosage required and the optimal time of commencement or by means of staple food fortification), identified by the WHO as a knowledge gap requiring an urgent response.[9]

We aimed to evaluate the effectiveness and safety of calcium for pre-eclampsia prevention, according to high (≥1 g/day) or low (<1 g/day) dose, and other population and intervention characteristics.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) network meta-analysis (NMA) checklist guided our reporting (Table S1). The protocol was prospectively registered (CRD42018111239).

Without language restrictions, we included in the meta-analysis randomised controlled trials (RCTs) of calcium supplementation in high or low dose, compared with placebo/no therapy, that enrolled women of reproductive age (15–49 years) in pre-pregnancy or during pregnancy, and reported the outcome of pre-eclampsia. In an NMA, we also included trials of different calcium doses, but excluded trials that provided calcium in the same dose to both intervention and control groups.

The primary outcome was pre-eclampsia, as defined by the trial authors.[1]

Secondary maternal outcomes included: haemolysis, elevated liver enzyme and low platelet (HELLP) syndrome; maternal death (during pregnancy or within 42 days of the end of the pregnancy); and severe maternal morbidity (including eclampsia, severe hypertension and other maternal complications, including stroke, pulmonary oedema, renal failure or hepatic failure, individually or as a composite of severe morbidity, as defined by authors), maternal intensive care, placental abruption, caesarean delivery, adherence and adverse events. Secondary fetal/newborn outcomes included: stillbirth (from 20^{+0} weeks of gestation); neonatal death; perinatal mortality (from 20^{+0} weeks of gestation to 7 days postnatally); preterm birth (<37^{+0} weeks of gestation); early preterm birth (<34^{+0} weeks, or as defined by the authors); low birthweight (<2500 g, or as defined by the authors); severe neonatal morbidity (admission to neonatal intensive care); and cost-effectiveness (for descriptive analysis).

The following core outcomes in pregnancy hypertension were not included: intubation or ventilation (other than for childbirth); postpartum haemorrhage; and newborn respiratory distress syndrome (or support) and seizures.[10]

Searches were conducted on Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, the WHO Global Index Medicus, including African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asia Region (IMSEAR), Latin America and the Caribbean Literature on Health Sciences (LILACS), and Western Pacific Index Medicus (WPRO), the Cumulative Index to Nursing and

Allied Health Literature (CINAHL), ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), from database inception to 2 February 2021. Searches used the terms 'calcium AND (eclampsia OR pre-eclampsia OR preeclampsia OR hypertension) AND pregnancy AND (trial OR random)', without language restriction. Additional articles were identified through handsearching the references of the included papers and previous systematic reviews, with input from content experts.

Two independent reviewers (CS and MWK) screened titles and abstracts and undertook the full-text review. Articles with unclear eligibility were discussed with LAM or PvD until consensus was reached.

Data were extracted by two reviewers (CS and MWK) in duplicate, using the Cochrane form for intervention reviews.[11] Data extracted comprised characteristics of studies, participants, the intervention and outcomes, taking an intention-to-treat approach. Pre-eclampsia risk (low vs high) was as reported by trial authors. Baseline calcium intake (low vs adequate) was considered low at <900 mg/day mean calcium intake,[7] among trial participants or in the study country.[12] Calcium timing was considered early if given before pregnancy or 20^{+0} weeks of gestation. Given the age of many of the studies, authors were not contacted for missing information.

Included trials were evaluated using the Cochrane risk-of-bias tool, which assessed: random sequence generation; allocation concealment; masking of participants, personnel and outcome assessment; incomplete outcome data; selective reporting; and other biases.[13] Overall, the risk of bias was considered low if the risk were low for all domains, high if the risk was high for at least one domain and otherwise unclear.

Data were summarised descriptively, and outcomes pooled using random-effects models and Review Manager (RevMan 5.3). Effect estimates were reported as risk ratio (RR) with 95% confidence interval (95% CI) for calcium versus placebo/no therapy. Heterogeneity was classified by I^2 as may not be important (<40%) or may represent moderate (30–60%), substantial (50–90%) or considerable (≥75%) heterogeneity.[13] The effect of calcium was evaluated by calcium dosage (high/low), pre-eclampsia risk (high/low), average baseline dietary calcium intake (adequate/low), intervention timing (early/late) and another intervention component. Certainty of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations),[14] for pre-eclampsia and subgroups of interest (as above).

Sensitivity analyses examined any potential imbalance (by funnel plot), according to study quality (restricted to those at low risk of bias)[13] and sample size (with <400 participants defined as small).[7]

The NMA aimed to compare high- and low-dose calcium, using a Bayesian random-effects model that synthesised direct and indirect estimates into an overall network effect. Direct estimates were obtained from head-to-head treatment comparisons excluded from our meta-analysis, whereas indirect estimates were computed by pooling data from a common comparator (placebo/no therapy), following confirmation that high-dose and low-dose (vs placebo/no therapy) trials do not differ with regards to the distribution of potential effect modifiers. The overall network effect was expressed as an RR and 95% credible interval (95% CrI). Uninformative priors were used at all points in this hierarchical process. Network meta-regression was performed independently for each moderator of interest (as for the meta-analysis).

Network visualisation was achieved by network plot, with nodes and edges scaled to represent the number of participants and comparisons, respectively. The overall network effect (vs placebo) used a forest plot with RR (95% CrI) for visualisation, and a league table of relative treatment effects. Heterogeneity was quantified for each main outcome by an overall inconsistency index between direct and indirect ORs, the Bayesian NMA version of I^2. A table of RR (95% CrI) values summarised the meta-regression results for all treatments of interest, with subgroup effects interpreted by the degree of overlap of 95% CrIs.

Analyses were performed using the BUGSnet package available in R statistical software (https://bugsnetsoftware.github.io/). $p < 0.05$ was considered statistically significant.

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The prior relevant Cochrane reviews had patient and public involvement embedded.[7,8] A James Lind Alliance Priority-Setting Partnership in pregnancy hypertension identified the prevention of pre-eclampsia as a top-10 research priority.[15] Patients were not directly involved in this review, but results were interpreted in light of trial participant characteristics, so that future care can be personalised.

3 | RESULTS

Of the 720 records identified, 30 RCTs (20 445 women) were eligible for the calcium supplementation versus placebo/no therapy meta-analysis[16–45]; and one additional RCT (272 women) was eligible for the high- versus low-dose calcium NMA (Figure S1).[46] Reasons for exclusion are detailed in Table S2, and included seven continuing trials.[47–53]

Trials of calcium versus placebo/no therapy were primarily from individual countries, usually in the Americas (Table 1); four trials were conducted in multiple countries, involving sites in Argentina, Bangladesh, Colombia, Egypt, India, Peru, South Africa, the USA, Vietnam and Zimbabwe.[24,25,42,44] Over three decades of trials (from 1987[33] to 2019[25]) enrolled a median of just under 200 women per trial (Table S3). One-third of trials were at high risk of bias

(Table S4), most often because of inadequate blinding (8/12 trials).

Most trials (N = 18) evaluated high-dose calcium, 11 trials evaluated low-dose calcium and another provided high- and low-dose arms,[18] each compared with placebo/no therapy (usually placebo); one trial compared high- and low-dose calcium directly, and was included only in the NMA.[46] Over half of the trials enrolled women considered to be at 'high risk' of developing pre-eclampsia, with at least one pre-eclampsia risk factor (Table 1). Most trials enrolled women with low baseline calcium intake; when evaluated, this was always post-randomisation or inferred from average intake data for the relevant population. Six trials initiated calcium supplementation before 20 weeks of gestation, although the 11 'late' calcium initiation trials began calcium not much later than 20 weeks of gestation. Median adherence to calcium was >80%, with non-adherence most frequently attributed to the large tablet size.

Additional components of the intervention were vitamin D,[17,26,27,33,38,41] aspirin (to controls[36,41] or to both groups[18]), linoleic acid[23,24] or antioxidants.[37]

All trials defined pre-eclampsia by new-onset hypertension and proteinuria at ≥20 weeks of gestation.[1]

TABLE 1 Baseline characteristics of the included trials of calcium supplementation versus placebo/no therapy and their participants; N (%) or median (range), unless otherwise stated

	N = 30[a] trials	References
Trial characteristics		
Year of publication	1998 (1987–2019)	16–45
Single-country sites	27 (90.0%)	
Americas	10	18,19,23,29–32,39,40,43
Eastern Mediterranean	6	17,22,27,34,38,41
South-East Asia	5	28,33,35,37,45
Western Pacific	5	16,20,21,26,36
N participants	180 (30–8325)	16–45
Risk of bias		
Low	9	23–25,29,37,39,40,43,44
High	11	16–18,20,22,26,27,33,36,41,45
Unclear	10	19,21,28,30–32,34,35,38,42
Characteristics of participants		
Pre-eclampsia risk (high[b])	17	16–18,22–27,31,32,34,36,38,39,43
Baseline calcium intake		
Adequate	6	21,27,29,38,42,43
Low	24	16–20,22–26,28,30–37,39–41,44,45
Measured in trial	15	19,22–25,28,30–33,35,39,40,44,45
Inferred from other data	9	16–18,20,26,34,36,37,41
Characteristics of intervention		
Calcium dose[c]		
High	18	18,19,21,22,27–32,34,35,38–40,42–45
Low	11	16–18,20,23–26,33,36,37,41
Timing of calcium initiation		
Early	6	16,25,28,29,37,44
Late	24	17–24,26,27,30–36,38–43,45
Adherence, median (IQR)	83% (78–88%) (N = 10 trials)	19,22–24,27–29,35,39,44
Characteristics of comparator		
Placebo	21	19,21–25,27–32,34,35,37–40,42–44
No therapy	8	16,18,20,26,33,36,41,45
Other therapy[c]	4	17,18,36,41

[a]These exclude one trial of high- versus low-dose calcium included in the NMA.[46]

[b]Pre-eclampsia risk factors included adolescent pregnancy, maternal age over 35 years, chronic underlying medical conditions, a family history and/or past history of pre-eclampsia, positive roll-over test or angiotensin sensitivity, abnormal uterine artery Doppler and/or high mean arterial pressure.

[c]High dose defined as ≥1 g elemental calcium/day; low dose defined as <1 g elemental calcium/day.

[d]One trial administered ferrous gluconate,[17] and three trials were multi-arm and provided an additional arm that compared calcium with low-dose aspirin.[18,36,41]

3.1 | Meta-analysis

Calcium supplementation (vs placebo/no therapy) was associated with a 51% reduction in pre-eclampsia incidence, with substantial between-trial heterogeneity (RR 0.49, 95% CI 0.39–0.61; 30 trials with 31 comparisons; 20 445 participants; I^2 = 59%). Effect estimates were almost identical for high- and low-dose calcium (vs placebo/no therapy), although heterogeneity remained; trials are displayed chronologically, without any obvious temporal trend in effect (Figure 1). Although there was substantial between-trial heterogeneity overall and for most subgroups (Figures S2–S5; Table 2), what appeared to be at issue was the magnitude of the effect, rather than whether there was an effect at all (Figure 1); the exception was the adequate baseline calcium intake subgroup, for which there was no significant effect of calcium on pre-eclampsia (Figure S3). The results were consistent regardless of whether low baseline calcium intake was assessed directly among trial participants (RR 0.52, 95% CI 0.38–0.70; 15 trials; 12 053 participants; I^2 = 62%) or indirectly from the general population (RR 0.39, 95% CI 0.27–0.55; nine trials; 2997 participants; I^2 = 30%). The certainty of evidence was moderate (or strong for late initiation of calcium), usually downgraded for heterogeneity and upgraded for large effect size (Tables 2 and S5).

The funnel plot was asymmetrical, with a preponderance of small studies (<400 participants) more likely to show a treatment effect of calcium on reduction in pre-eclampsia risk (Figure S6)[17,20,23,24,27,30–32,34–40,42,43,45]; calcium remained effective following the exclusion of these studies (RR 0.59, 95% CI 0.46–0.76; 11 trials; 18 487 participants; I^2 = 73%) (Figure S7) or only among trials at low risk of bias (RR 0.68, 95%CI 0.52–0.89; nine trials; 13 964 participants, I^2 = 60%) (Figure S8).

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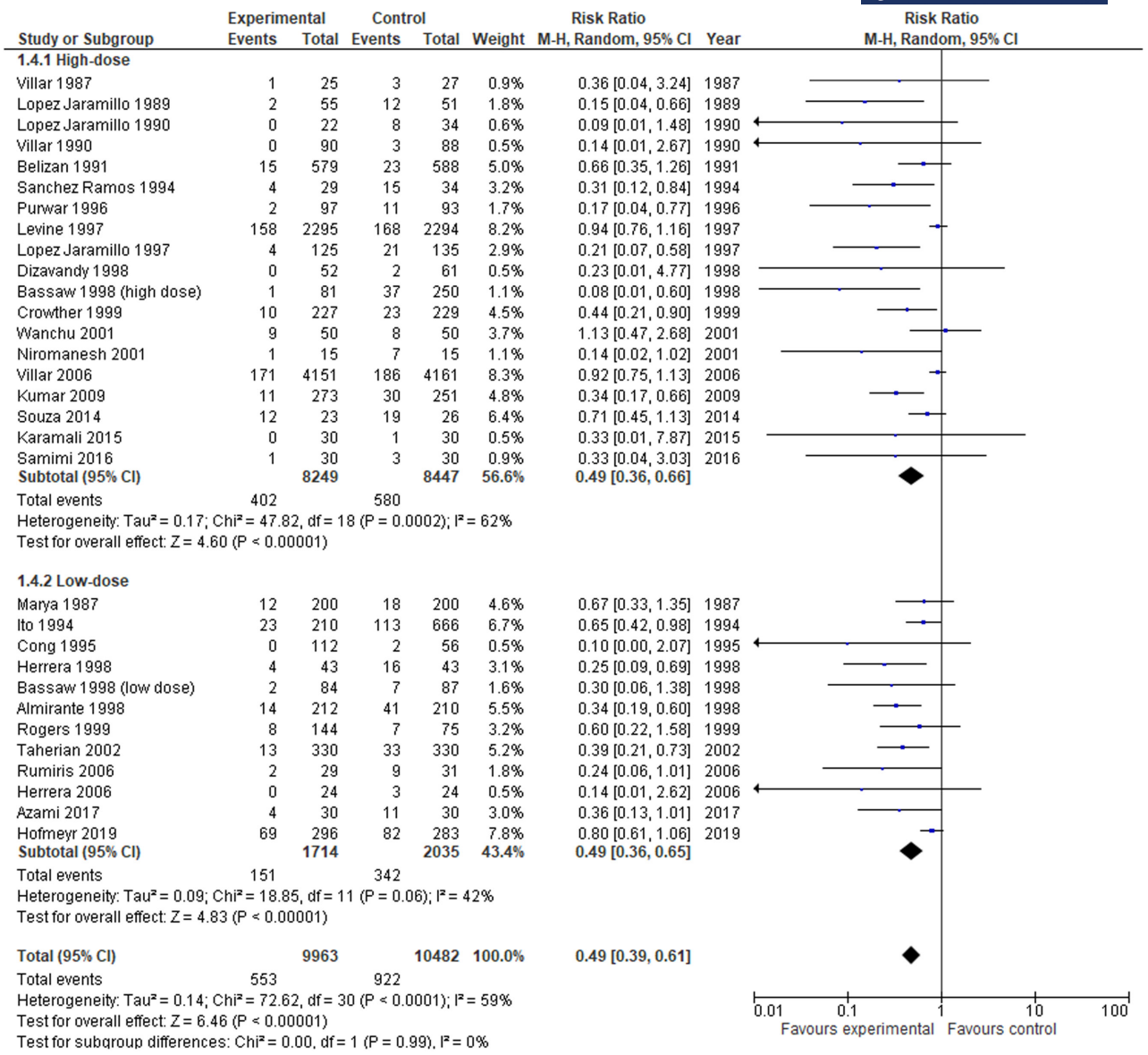

FIGURE 1 Risk ratio (RR) and 95% confidence interval (95% CI) for the effect of calcium supplementation versus placebo/no therapy on the incidence of pre-eclampsia, according to dose.

Despite doubling the incidence of HELLP syndrome (to 26/6515, 0.40%, from 13/6536, 0.20%), calcium significantly and consistently decreased the incidence of composite severe maternal morbidity (to 228/4447, 5.1%, from 272/4444, 6.1%) (Table 2), preterm birth (to 908/8676, 10.5%, from 994/8687, 11.4%) and low birthweight (to 898/7761, 11.6%, from 974/7753, 12.6%). Calcium had no effect on other outcomes. Maternal deaths complicated 59/100 000 identified pregnancies (3/5053) in the calcium groups and 158/100 000 (8/5059) in the placebo groups.[19,25,44]

Half of the trials (16/31) reported on the rate of adverse events, with 13/16 reporting none. Three trials reported primarily gastrointestinal adverse effects with similar frequency in calcium and placebo/no therapy groups; the high-dose trial reported nausea, vomiting and abdominal pain,[21] and the low-dose trial reported symptoms such as flatulence or gastritis.[24] Another high-dose trial reported rare (<1%) nephrolithiasis and renal colic.[44]

No trial reported a cost-effectiveness or cost-consequences analysis of calcium supplementation.

3.2 | Network meta-analysis

The NMA (25 trials, 15 038 women) included 24 trials in the meta-analysis (details presented in Table 1), plus a trial of 2000 mg/day versus 500 mg/day elemental calcium from 20 weeks of gestation, in healthy nulliparous women (at low risk), with low baseline calcium intake in India.[46] Trials of high-dose and low-dose calcium, with roughly similar frequency, enrolled women at high risk (trials[18,22,27,31,32,34,38,39,43] with high dose; trials[16–18,23–26,36] with low dose) or women at low risk (trials[19,21,28–30,35,42,44–46] with high dose; trials[20,33,37,41and46] with low dose) of pre-eclampsia, women with a low average baseline dietary intake of calcium (trials[18,19,22,28,30–32,34,35,39,40,44–46] with

TABLE 2 Summary of findings for trials of calcium supplementation (vs placebo/no therapy)

	N comparisons	*N* participants	Risk ratio (95% CI)[a]	I^2[a]	Certainty of evidence (GRADE)[b]
Maternal outcomes					
Pre-eclampsia (any)[c]	31	20 445	0.49 (0.39–0.61)	59%	⊕⊕⊕O
High-dose calcium[c]	19	16 696	0.49 (0.36–0.66)	62%	⊕⊕⊕O
Low-dose calcium[c]	12	3749	0·49 (0.36–0.65)	42%	⊕⊕⊕O
Adequate baseline calcium	6	5395	0.62 (0.37–1.06)	31%	⊕⊕⊕O
Low baseline calcium intake	24	15 050	0.45 (0.35–0.58)	63%	⊕⊕⊕O
High pre-eclampsia risk	17	3661	0.41 (0.29–0.57)	51%	⊕⊕⊕O
Low pre-eclampsia risk	13	16 784	0.46 (0.42–0.76)	64%	⊕⊕⊕O
Calcium pre-/early pregnancy	6	14 486	0.66 (0.48–0.90)	77%	⊕⊕⊕O
Calcium from late pregnancy	24	5959	0.43 (0.33–0.56)	32%	⊕⊕⊕⊕
Added intervention[c]	11	2530	0.54 (0.42–0.68)	0%	⊕⊕⊕O
No added intervention[c]	20	17 915	0.49 (0.37–0.65)	67%	⊕⊕⊕O
Maternal death	3	10 112	0.42 (0.07–2.39)	31%	—
HELLP syndrome	3	13 051	2.09 (1.09–4.02)	0%	—
Eclampsia	7	14 411	0.70 (0.42–1.17)	0%	—
Severe maternal morbidity	2	8891	0.84 (0.71–0.99)	0%	—
Severe hypertension	4	13 936	0.89 (0.74–1.07)	0%	—
Stroke	2	5168	1.00 (0.14–7.09)	NA	—
Pulmonary oedema	1	5 79	0.32 (0.01–7.79)	NA	—
Renal failure	2	4715	1.04 (0.62–1.75)	0%	—
Hepatic failure	1	116	1.36 (0.53–3.50)	–	—
Maternal intensive care	3	8951	0.83 (0.65–1.05)	0%	—
Caesarean delivery	17	17 574	1.00 (0.88–1.13)	51%	—
Placental abruption	6	15 235	0.98 (0.65–1.48)	0%	—
Perinatal outcomes					
Perinatal mortality	5	6393	0.91 (0.61–1.37)	0%	—
Stillbirth	11	15 679	0.89 (0.72–1.10)	0%	—
Neonatal death	3	13 000	1.02 (0.47–2.22)	47%	—
Birth at $<37^{+0}$ weeks of gestation	19	17 363	0.82 (0.69–0.98)	47%	—
Birth at $<34^{+0}$ weeks of gestation	6	14 328	0.89 (0.73–1.08)	14%	—
Small-for-gestational age	12	14 906	1.01 (0.86–1.20)	0%	—
Low birthweight	13	15 514	0.85 (0.74–0.99)	37%	—
Admission to neonatal care unit	6	13 825	0.86 (0.66–1.13)	65%	—

Abbreviations: HELLP, Haemolysis, Elevated Liver Enzyme, Low Platelet syndrome.

[a]Effect size calculations were based on a random-effects model. Heterogeneity, assessed by I^2, was classed as: may not be important (<40%); moderate (30–60%); substantial (50–90%); or considerable (≥75%).

[b]Certainty was high ⊕⊕⊕⊕, moderate ⊕⊕⊕O, low ⊕⊕OO, or very low OOOO (see Table S6).

[c]One multi-arm trial contributed to each comparison.[18]

high dose; trials[16–18,20,23–26,33,36,37,41,46] with low dose) and women who initiated calcium supplementation early (trials[28,29,44] with high dose; trials[16,25,37] with low dose) or late (trials[18,19,21,22,27,30–32,34,35,38–40,42–46] with high dose; trials[17,18,20,23,24,26,33,36,41,46] with low dose) in pregnancy. The six trials among populations with adequate average calcium intake (trials[21,27,29,38,42,43]) were not included in the NMA because they were all were high-dose calcium trials and their inclusion would have violated the assumption of transitivity.

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The network plot reflects a reliance almost entirely on indirect evidence (Figure S9), precluding the calculation of an inconsistency index. There was no significant impact on pre-eclampsia of -high versus low-dose calcium supplementation (RR 0.79, 95% CrI 0.43–1.40) (Figure S10); however, findings were consistent with a 57% decrease or 40% increase in pre-eclampsia risk with high-dose calcium (vs low-dose calcium). By meta-regression, high- and low-dose calcium were similarly effective overall, based on the substantial overlap of the wide 95% CrI, by high or low baseline pre-eclampsia risk, low baseline calcium intake, early or late timing of initiation of calcium and with or without additional therapy (yes/no) (Figure 2); adequate average baseline calcium intake was not evaluated as these women were enrolled only in high-dose trials.

We performed post-hoc sensitivity analyses with the inclusion of the six adequate-intake trials because: (i) baseline calcium intake was presented at study level, as average intake; (ii) baseline calcium intake was not measured directly within the study population, but determined by population figures in 10 trials; and (iii) when baseline calcium intake was measured in a trial, it was always post-randomisation. The sensitivity analysis including all 31 trials similarly found no significant impact of high- versus low-dose calcium (RR 0.83, 95% CI 0.47–1.43) (Figure S11).

4 | DISCUSSION

4.1 | Main findings

Using direct and indirect trial evidence in meta-analysis and NMA, calcium supplementation (vs placebo/no therapy) decreases the incidence of pre-eclampsia, defined traditionally as gestational hypertension and new proteinuria. This effect is similar with high- or low-dose calcium, regardless of baseline pre-eclampsia risk, timing of calcium initiation or co-interventions (particularly vitamin D); however, the effectiveness of calcium is restricted to populations with low average baseline calcium intake. The small increase (of an absolute 0.2%) in HELLP syndrome with calcium was more than balanced by a reduced incidence of death or severe maternal morbidity (by 1.0%). Although calcium does not conclusively reduce preterm pre-eclampsia, it does reduce the incidence of preterm birth and infants with low birthweight.

4.2 | Strengths and limitations

The strengths of this study include a comprehensive literature search for all relevant RCTs, including high- versus low-dose calcium included in the NMA. We considered

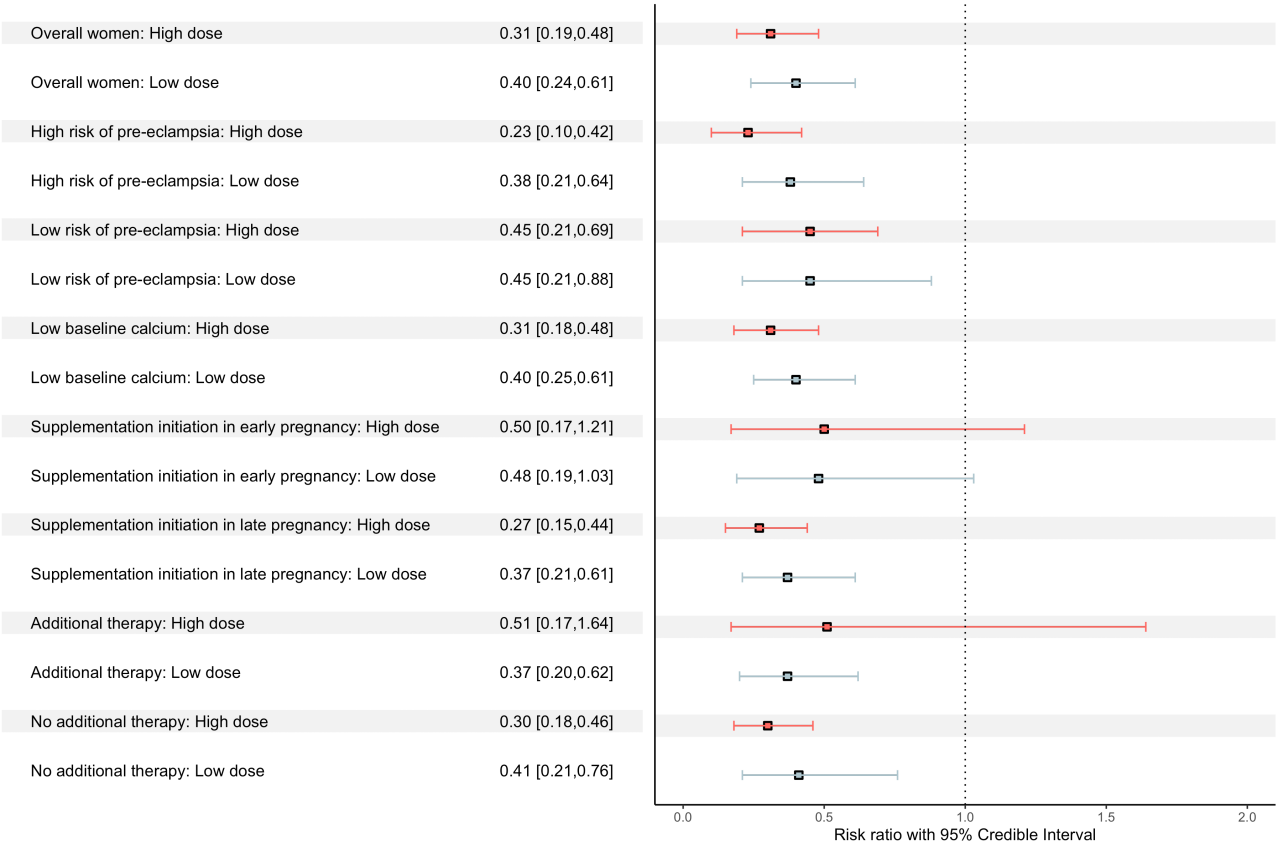

FIGURE 2 Network meta-regression of treatments compared with placebo.

effect moderation by trial location and by maternal and intervention characteristics. We reported on a broad range of outcomes and considered core outcomes for pre-eclampsia.[10] Finally, our NMA results both inform the comparison between high- and low-dose calcium (by integrating scant direct evidence with that provided through the placebo/no therapy node of the network) and calcium effectiveness in subgroups for which direct trial evidence was lacking (including low-dose calcium for women with adequate calcium intake).

Limitations include the retrospective nature of the meta-analysis, and constraints of the primary literature, including publication bias. Many trials were >20 years old, making individual participant data meta-analysis unfeasible to deal with individual-level moderation. The timing-of-initiation analyses were based on limited information about calcium initiation before pregnancy or in the first trimester, and the trial that began calcium supplementation pre-pregnancy underestimated the benefit of early (and continuing) supplementation, because high-dose calcium was administered to all women from 20 weeks of gestation, thereby 'cancelling out' the effect of the early calcium initiation.[25] Few trials reported adverse effects, although follow-up was usually limited to immediately postpartum. There were core outcomes for pre-eclampsia for which little or no data were available. No trial published a health economics analysis. Some trials did not include baseline calcium intake assessment.

4.3 | Interpretation (in light of other evidence)

Our finding that high- and low-dose calcium each halve the risk of pre-eclampsia is consistent with the most recent Cochrane review that included fewer trials (N = 22) and found large risk reductions in pre-eclampsia with high-dose calcium (RR 0.45, 95% CI 0.31–0.65; 13 trials; 15 730 participants) and low-dose calcium (RR 0.38, 95% CI 0.28–0.52; nine studies; 2234 participants),[7] and a similar doubling of HELLP (RR 2.67, 95% CI 1.05–6.82; two studies; 12 901 participants).[7] We included the international CAP Trial, which is in a separate Cochrane Review,[25] and that uniquely administered low-dose calcium before pregnancy and continued into early pregnancy, with a significant reduction in pre-eclampsia among women adherent to the intervention; this supports a food fortification approach to dietary calcium deficiency.[25]

There are two prior NMAs of calcium supplementation for pre-eclampsia prevention. The first focused on the relative effectiveness of calcium and vitamin D, without addressing calcium dosage; calcium was effective (vs placebo/no therapy) and the possibility was raised that vitamin D alone may also be effective.[54] The second NMA was not prospectively registered, included fewer (N = 24) English language trials than our NMA and evaluated calcium dosage only by baseline pre-eclampsia risk, but excluding the seven low-dose calcium, high-baseline pre-eclampsia risk trials, making their findings that low-dose calcium was not effective difficult to interpret.[16,17,23–26,36,55]

Although we found that high- and low-dose calcium are similarly effective in decreasing the incidence of pre-eclampsia, the 95% CrI includes clinically important benefit (55% reduced odds) and harm (75% increased odds), without strong signals that there are women more likely to benefit (or be harmed) or that there is a type of administration more likely to maximise the effect. There are two continuing trials of high- versus low-dose calcium supplementation in countries with low baseline calcium intake.[49,50] Our findings do not suggest any superiority of high- over low-dose calcium, and high-dose calcium is not a feasible intervention in most LMICs. High-dose calcium can be four to five times the dose of low-dose calcium, which even at 500 mg/day is a large tablet presenting financial challenges as well as challenges for transport and storage. The effectiveness of low-dose calcium (vs high-dose calcium), and the apparent similar effectiveness (vs placebo/no therapy) when initiated after (vs before) 20 weeks of gestation, suggests that lower dosages than recommended by the WHO (1.5–2.0 g/day) may improve implementation and compliance,[9] and make staple food fortification an option.[56]

Neither high- nor low-dose calcium supplementation was associated with short-term harms. However, findings from rural Gambia highlight the need for longitudinal studies; there, where baseline calcium intake was low, 1500 mg/day of calcium during pregnancy was associated with lower maternal bone mineral content and recovery at 1 year postpartum.[57] These findings may reflect an abrupt alteration in calcium homeostasis through the withdrawal of high-dose calcium postpartum and a return to very low habitual dietary calcium intake.[57] No study reported on the potentially negative impact of calcium on iron absorption, particularly for high-dose calcium taken three times per day,[56] although there is no compelling evidence of a long-term impact on iron status.[58]

The very small increase in HELLP was more than balanced by the fewer maternal deaths, maternal near-miss events and adverse perinatal outcomes. Although concern has been raised that calcium may mask pre-eclampsia until presentation as HELLP, through its effect in lowering blood pressure,[59] the fact that blood pressure control with antihypertensive therapy may actually reduce the development of low platelets and elevated liver enzymes would argue against this, and lowering blood pressure does not reduce the risk of developing proteinuria.[60] Other potential mechanisms include the mitigation of metabolic changes associated with low dietary calcium intake, including: an increase in parathyroid hormone (that increases intracellular calcium in vascular smooth muscle cells and leads to vasoconstriction),[56] an increase in the synthesis of calcitriol that stimulates the renin–angiotensin–aldosterone system and the expansion of intravascular volume,[61,62] or low-grade systemic inflammation and insulin resistance.[61]

Few trials included aspirin in the intervention or control arms, yielding insufficient evidence to evaluate the additive or comparative effects of calcium and aspirin. However, our data suggest that the most important modifier of calcium effectiveness is baseline calcium intake and not pre-eclampsia risk, which would make calcium and aspirin potentially complementary preventative strategies. Of note, the effect estimate for calcium (52% relative risk reduction for women with low baseline calcium intake) far exceeds that for aspirin (17% relative risk reduction in any pre-eclampsia for women at increased pre-eclampsia risk based on clinical factors, or a 62% reduction in preterm pre-eclampsia for women at high risk by multivariable first-trimester screening),[5,63] and low calcium intake is more common (e.g. at least 50% of adult women, where the median intake is 682 mg/day; 2008–2009)[64] than increased pre-eclampsia risk (e.g. 10% by multivariable first trimester screening).[5,63]

5 | CONCLUSION

Low-dose calcium is as effective for pre-eclampsia prevention as the high-dose calcium supplementation recommended by the WHO. Calcium should be reserved for women with low calcium intake, assessed at a population level in LMICs and individually in high-income countries. Calcium is a complementary approach to the early multifactor screening and aspirin use that prevents 60% of preterm pre-eclampsia, but not the 70% of disease that arises at term; calcium is equally effective at reducing both preterm and term pre-eclampsia in women with low calcium intake. Future research should focus on how to implement this intervention where average calcium intake is low, and where it is not, how best to identify and target women with low calcium intake women for personalised pre-eclampsia prevention in the second half of pregnancy.

AUTHOR CONTRIBUTIONS

PvD, LAM and GJH conceptualised the review. MWK and CS conducted the review and conducted the statistical analyses with AS and JNB. MWK, CS, LAM and PvD wrote the first draft of the article. MV, SEM, RE, GC, JB, GJH, LAM and PvD reviewed all versions of the article and contributed to the interpretation and the structure of the review. All authors read and approved the final version for publication.

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CONFLICT OF INTERESTS

GJH is an author of two of the trials included in the meta-analysis. GJH was involved in neither the study selection, data extraction nor analysis. All other authors declare no competing interests. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

DETAILS OF ETHICS APPROVAL

The review only used data from previous published studies.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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