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Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (Review)

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[Intervention Review]

Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

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ABSTRACT

Background

Pre-eclampsia and eclampsia are common causes of serious morbidity and death. Calcium supplementation may reduce the risk of pre-eclampsia, and may help to prevent preterm birth. This is an update of a review last published in 2014.

Objectives

To assess the effects of calcium supplementation during pregnancy on hypertensive disorders of pregnancy and related maternal and child outcomes.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (18 September 2017), and reference lists of retrieved studies.

Selection criteria

We included randomised controlled trials (RCTs), including cluster-randomised trials, comparing high-dose calcium supplementation (at least 1 g daily of calcium) during pregnancy with placebo. For low-dose calcium we included quasi-randomised trials, trials without placebo, trials with cointerventions and dose comparison trials.

Data collection and analysis

Two researchers independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. Two researchers assessed the evidence using the GRADE approach.

Main results

We included 27 studies (18,064 women). We assessed the included studies as being at low risk of bias, although bias was frequently difficult to assess due to poor reporting and inadequate information on methods.

High-dose calcium supplementation (≥ 1 g/day) versus placebo

Fourteen studies examined this comparison, however one study contributed no data. The 13 studies contributed data from 15,730 women to our meta-analyses. The average risk of high blood pressure (BP) was reduced with calcium supplementation compared with placebo (12 trials, 15,470 women: risk ratio (RR) 0.65, 95% confidence interval (CI) 0.53 to 0.81; I^2 = 74%). There was also a reduction in the risk of pre-eclampsia associated with calcium supplementation (13 trials, 15,730 women: average RR 0.45, 95% CI 0.31 to 0.65; I^2 = 70%; low-quality evidence). This effect was clear for women with low calcium diets (eight trials, 10,678 women: average RR 0.36, 95% CI 0.20 to 0.65; I^2 = 76%) but not those with adequate calcium diets. The effect appeared to be greater for women at higher risk of pre-eclampsia, though this may be due to small-study effects (five trials, 587 women: average RR 0.22, 95% CI 0.12 to 0.42). These data should be interpreted with caution because of the possibility of small-study effects or publication bias. In the largest trial, the reduction in pre-eclampsia was modest (8%) and the CI included the possibility of no effect.

The composite outcome maternal death or serious morbidity was reduced with calcium supplementation (four trials, 9732 women; RR 0.80, 95% CI 0.66 to 0.98). Maternal deaths were no different (one trial of 8312 women: one death in the calcium group versus six in the placebo group). There was an anomalous increase in the risk of HELLP syndrome in the calcium group (two trials, 12,901 women: RR 2.67, 95% CI 1.05 to 6.82, high-quality evidence), however, the absolute number of events was low (16 versus six).

The average risk of preterm birth was reduced in the calcium supplementation group (11 trials, 15,275 women: RR 0.76, 95% CI 0.60 to 0.97; I^2 = 60%; low-quality evidence); this reduction was greatest amongst women at higher risk of developing pre-eclampsia (four trials, 568 women: average RR 0.45, 95% CI 0.24 to 0.83; I^2 = 60%). Again, these data should be interpreted with caution because of the possibility of small-study effects or publication bias. There was no clear effect on admission to neonatal intensive care. There was also no clear effect on the risk of stillbirth or infant death before discharge from hospital (11 trials, 15,665 babies: RR 0.90, 95% CI 0.74 to 1.09).

One study showed a reduction in childhood systolic BP greater than 95th percentile among children exposed to calcium supplementation in utero (514 children: RR 0.59, 95% CI 0.39 to 0.91). In a subset of these children, dental caries at 12 years old was also reduced (195 children, RR 0.73, 95% CI 0.62 to 0.87).

Low-dose calcium supplementation (< 1 g/day) versus placebo or no treatment

Twelve trials (2334 women) evaluated low-dose (usually 500 mg daily) supplementation with calcium alone (four trials) or in association with vitamin D (five trials), linoleic acid (two trials), or antioxidants (one trial). Most studies recruited women at high risk for pre-eclampsia, and were at high risk of bias, thus the results should be interpreted with caution. Supplementation with low doses of calcium reduced the risk of pre-eclampsia (nine trials, 2234 women: RR 0.38, 95% CI 0.28 to 0.52). There was also a reduction in high BP (five trials, 665 women: RR 0.53, 95% CI 0.38 to 0.74), admission to neonatal intensive care unit (one trial, 422 women, RR 0.44, 95% CI 0.20 to 0.99), but not preterm birth (six trials, 1290 women, average RR 0.83, 95% CI 0.34 to 2.03), or stillbirth or death before discharge (five trials, 1025 babies, RR 0.48, 95% CI 0.14 to 1.67).

High-dose (=/> 1 g) versus low-dose (< 1 g) calcium supplementation

We included one trial with 262 women, the results of which should be interpreted with caution due to unclear risk of bias. Risk of pre-eclampsia appeared to be reduced in the high-dose group (RR 0.42, 95% CI 0.18 to 0.96). No other differences were found (preterm birth: RR 0.31, 95% CI 0.09 to 1.08; eclampsia: RR 0.32, 95% CI 0.07 to 1.53; stillbirth: RR 0.48, 95% CI 0.13 to 1.83).

Authors' conclusions

High-dose calcium supplementation (≥ 1 g/day) may reduce the risk of pre-eclampsia and preterm birth, particularly for women with low calcium diets (low-quality evidence). The treatment effect may be overestimated due to small-study effects or publication bias. It reduces the occurrence of the composite outcome 'maternal death or serious morbidity', but not stillbirth or neonatal high care admission. There was an increased risk of HELLP syndrome with calcium supplementation, which was small in absolute numbers.

The limited evidence on low-dose calcium supplementation suggests a reduction in pre-eclampsia, hypertension and admission to neonatal high care, but needs to be confirmed by larger, high-quality trials.

PLAIN LANGUAGE SUMMARY

Calcium supplementation during pregnancy for preventing blood pressure disorders and related problems

What is the issue?

Pre-eclampsia is evident as high blood pressure and protein in the urine. It is a major cause of death in pregnant women and newborn babies worldwide. Preterm birth (birth before 37 weeks) is often caused by high blood pressure and is the leading cause of newborn deaths, particularly in low-income countries.

Why is this important?

Evidence from randomised controlled trials shows that calcium supplements help prevent pre-eclampsia and preterm birth and lower the risk of a woman dying or having serious problems related to high blood pressure in pregnancy. This is particularly for women on low calcium diets.

What evidence did we find?

We searched for evidence on 18 September 2017, and found 27 trials. We found evidence from 13 studies (involving 15,730 women) that calcium supplementation in high doses (at least 1 gram (g) daily) during pregnancy may be a safe way of reducing the risk of pre-eclampsia, especially in women from communities with low dietary calcium and those at increased risk of pre-eclampsia. Women receiving calcium supplements may also be less likely to die or have serious problems related to pre-eclampsia (low-quality evidence) and high blood pressure. Babies may be less likely to be born preterm (low-quality evidence). The syndrome of haemolysis, elevated liver enzymes and low platelets was increased with calcium, but the absolute numbers were small (high-quality evidence). High-dose calcium did not have a clear effect on babies admitted to neonatal intensive care, or the number of stillbirths or deaths before discharge from hospital.

Further research is needed into the ideal dosage of supplementation. Limited evidence from 12 trials (2334 women) suggested that a relatively low dose of calcium may be effective in reducing pre-eclampsia, high blood pressure, and babies admitted to intensive care (however, the quality of the evidence on calcium alone was reduced because eight of the included trials gave other medicines alongside calcium, such as vitamin D, linoleic acid or antioxidants). Low-dose calcium did not have a clear effect on preterm birth, stillbirth or death before discharge from hospital.

One small study compared high-dose calcium with low-dose calcium. Pre-eclampsia appeared to be reduced in the high-dose group, but no other differences were found in preterm birth, or stillbirth.

What does this mean?

In settings where dietary calcium is low, supplementation is an important strategy to reduce the serious consequences of pre-eclampsia. Where high-dose supplementation is not feasible, the option of lower dose supplements (500 milligrams (mg) to 600 mg daily) might be considered in preference to no supplementation.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Calcium supplementation compared with placebo for preventing hypertensive disorders and related problems in pregnancy						
Patient or population: pregnant women **Settings:** outpatient **Intervention:** high-dose calcium (≥ 1 g/day) **Comparison:** placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	No calcium	**Calcium**				
Pre-eclampsia	**Overall**					
	65 per 1000	**29 per 1000** (20 to 42)	**RR 0.45** (0.31 to 0.65)	15,730 (13)	⊕⊕⊝⊝ low[1]	
	Low-calcium diet					
	57 per 1000	**21 per 1000** (11 to 37)	**RR 0.36** (0.20 to 0.65)	10,678 (8)	⊕⊕⊝⊝ low[1]	
	High-risk women					
	176 per 1000	**38 per 1000** (21 to 74)	**RR 0.22** (0.12 to 0.42)	587 (5)	⊕⊕⊝⊝ low[1]	
Preterm birth	**Overall**					
	104 per 1000	**79 per 1000** (62 to 101)	**RR 0.76** (0.60 to 0.97)	15,275 (11)	⊕⊕⊝⊝ low[1]	
HELLP syndrome	**1 per 1000**	**3 per 1000**	**RR 2.67** (1.05 to 6.82)	12,901 (2)	⊕⊕⊕⊕ high	

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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[1] Downgraded two levels due to heterogeneity and small study effects (-2)
CI: confidence interval
HELLP: haemolysis, elevated liver enzymes and low platelets
RR: risk ratio

BACKGROUND

Description of the condition

High blood pressure, with or without proteinuria, is a major cause of maternal death and morbidity (Betrán 2005; Clark 2008; HMSO 1994; Khan 2006; NHMRC 1993), and perinatal morbidity and mortality (Langenveld 2011; Ozkan 2011), worldwide. Hypertension has been estimated to complicate 5% of all pregnancies and 11% of first pregnancies, half associated with pre-eclampsia, and to account for up to 40,000 maternal deaths annually (Villar 2004). For this reason, strategies to reduce the risk of hypertensive disorders of pregnancy have received considerable attention (Bucher 1996; Carroli 1994; CLASP 1994; ECCPA 1996).

Spontaneous and medically induced preterm birth is commonly associated with hypertensive disorders. It is the leading cause of early neonatal death and infant mortality, particularly in low-income countries (Villar 1994). Preterm survivors are at high risk of significant morbidity, especially respiratory disease and its sequelae, and long-term neurological morbidity (Johnson 1993). Interventions to reduce preterm birth have been reviewed by Villar and colleagues (Villar 1998).

During early pregnancy, blood pressure normally falls; it then climbs slowly in later pregnancy to reach pre-pregnancy levels at term (Villar 1989). These normal changes in blood pressure make the diagnosis of hypertension during pregnancy difficult. Clinical methods of measuring blood pressure are also subject to considerable inaccuracy (Villar 2004). A widely accepted definition, however, is a diastolic blood pressure equal to or greater than 90 millimetres of mercury (mmHg) or systolic pressure equal to or greater than 140 mmHg before the onset of labour (NHBPEP 2000). The consequences of high blood pressure are more serious if there is associated proteinuria. Hypertension and significant proteinuria (1+ by dipstick testing, equal to or greater than 300 mg per 24 hours, or equal to or greater than 30 mg per decilitre (dL)) (NHBPEP 2000), usually indicate the presence of pre-eclampsia. The urine protein to creatinine ratio has been used increasingly as a measure of proteinuria (Yamasmit 2004). Predictors of poor outcome include low gestational age and high levels of proteinuria (von Dadelszen 2004).

Description of the intervention

Calcium supplementation is an oral dietary supplement, usually in the form of calcium carbonate or calcium gluconate. The dose is expressed in terms of the amount of elemental calcium in the preparation.

How the intervention might work

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980 (Belizan 1980). This was based on the observation that Mayan Indians in Guatemala, who traditionally soak their corn in lime before cooking, had a high calcium intake and a low incidence of pre-eclampsia and eclampsia. A very low prevalence of pre-eclampsia had been reported from Ethiopia where the diet, among other features, contained high levels of calcium (Hamlin 1962). These observations were supported by other epidemiological and clinical studies (Belizan 1988; Hamlin 1952; Repke 1991; Villar 1983; Villar 1987; Villar 1993), and led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and pre-eclampsia among women with low calcium intake. An association has been found between pre-eclampsia and hypocalciuria (Segovia 2004); lower urine calcium to creatinine ratio (Kazerooni 2003); hypocalcaemia (Kumru 2003); lower plasma and higher membranous calcium (Kisters 2000); lower dietary milk intake (Duvekot 2002); and between eclampsia and hypocalcaemia (Isezuo 2004).

Low calcium intake may cause high blood pressure by stimulating either parathyroid hormone or renin release, thereby increasing intracellular calcium in vascular smooth muscle (Belizan 1988), and leading to vasoconstriction. A possible mode of action for calcium supplementation is that it reduces parathyroid release and intracellular calcium, and so reduces smooth muscle contractility. By a similar mechanism, calcium supplementation could also reduce uterine smooth muscle contractility and prevent preterm labour and delivery (Villar 1990). Calcium might also have an indirect effect on smooth muscle function by increasing magnesium levels (Repke 1989). Recent evidence indicates that calcium supplementation affects uteroplacental blood flow (it lowers the resistance index in uterine and umbilical arteries) (Carroli 2010). Supplementation in the second half of pregnancy appears to reduce blood pressure directly, rather than preventing the endothelial damage associated with pre-eclampsia (Hofmeyr 2008).

Calcium supplementation is attractive as a potential intervention to reduce the risk of a woman developing pre-eclampsia as it is readily available, and is likely to be safe for the woman and her child. In addition, there is a possibility that it may have a preventative effect on the risk of hypertension in offspring (Belizan 1997). A theoretical risk of increased renal tract stone formation, or the occurrence of other adverse effects associated with calcium supplementation, has not been substantiated.

Why it is important to do this review

Calcium supplementation was tested in several randomised trials, commencing in the late 1980s, which suggested a promising beneficial effect on hypertensive disorders and related problems. The first systematic reviews highlighted the need for larger trials to assess the effects on important clinical outcomes in addition to pre-eclampsia and preterm delivery, such as perinatal mortality (Carroli 1994; Duley 1995). A subsequent systematic review came to more promising conclusions (Bucher 1996), but these findings were not confirmed by a large trial in the USA (CPEP 1997), and the discrepancy elicited discussion (Villar 2000). Subsequently, a large trial conducted in communities with low dietary calcium intake has been reported (WHO 2006). In 2012 the World Health Organization (WHO) published guidelines recommending calcium supplementation with 1.5 g to 2 g elemental calcium daily for pregnant women with low dietary calcium. This recommendation has raised questions regarding the optimum dosage of calcium.

1. The WHO recommendation was based on available data from randomised trials. Most of the high-quality trials reviewed used 1.5 g to 2 g of calcium daily, and there was little robust evidence regarding smaller dosages.
2. The dosage of 1.5 g to 2 g calcium daily is well above the daily recommended dietary calcium of 1 g to 1.2 g.
3. Logistically, calcium in this dosage is heavy to transport. Calcium carbonate plus glycine tablets containing 1.5 g elemental calcium and glycine daily (= 3750 mg calcium carbonate plus

glycine) weigh about 200 g for a four-week supply (84 tablets). This would amount to about 1 kg of tablets for 20 weeks, therefore, a clinic seeing 1000 pregnant women per year would need to receive 1000 kg of tablets each year.

4. The cost of calcium is moderately high (compared with supplements such as iron and folate), and the dosage thus has important cost implications.
5. A 2010 report from the Gambia study (Jarjou 2004) has suggested that calcium at the dosage of 1.5 g daily during pregnancy may impair the mother's ability to conserve calcium, causing rebound bone demineralisation following pregnancy. Although there are limitations to this study (conclusions were based on a sub-set of women from the original trial; the hypothesis was not prespecified; multiple end-point testing), the possibility of adverse effects due to the interruption of high-dose calcium supplementation in women who have previously adapted to low dietary calcium intake is reason for caution.

For these reasons, when updating this review, we considered it important to systematically review the evidence on lower dosages of calcium supplementation in pregnancy. Originally, we had specified that randomised controlled trials with dosages below 1 g daily would be reviewed in subsequent updates of this review. However, in view of the lack of high-quality trials of lower dosages, we revised the review to include lower quality studies (e.g. quasi-randomised trials) of lower dosage studies only.

This is an update of a review last published in 2014.

OBJECTIVES

To assess the effects of calcium supplementation during pregnancy on hypertensive disorders of pregnancy and related maternal and child outcomes.

Subgroup analyses tested whether these effects were influenced by whether:

1. women had low or adequate dietary calcium intake prior to trial entry;
2. women were at low or average risk of hypertensive disorders, or at high risk.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials. We included trials that were presented only as abstracts if there was sufficient detail (published and unpublished) to confirm eligibility. For the original review of high-dose calcium supplementation we excluded quasi-random designs. However, for the 2012 update we included trials employing these weaker study designs (e.g. quasi-randomisation by alternation, unstated or other methods), only for the subgroup of trials of calcium supplementation less than 1 g daily (low dose), with appropriate caution in the interpretation of the results. The reason for the discrepancy between high-dose and low-dose trials is that there are adequate data from appropriately randomised, placebo controlled trials of high-dose but not low-dose calcium supplementation for review. Cluster-randomised trials were also eligible for inclusion.

Because of the addition of a comparison of trials of low-dose calcium supplementation, it was also of interest to include trials comparing high- with low-dose supplementation. Please see Differences between protocol and review for details.

Types of participants

Pregnant women, regardless of the risk of hypertensive disorders of pregnancy. We excluded women with diagnosed hypertensive disorders of pregnancy. We did not exclude women with multiple pregnancy.

Prespecified subgroups to be compared were as follows.

1. Women at low or average risk of hypertensive disorders of pregnancy (unselected)
2. Women at above average risk of hypertensive disorders of pregnancy. These included women selected by the trial authors on the basis of an increased risk of hypertensive disorders of pregnancy (e.g. teenagers or women older than 40 years, women with previous pre-eclampsia, women with increased sensitivity to angiotensin II, women with pre-existing hypertension). Primiparity alone was not regarded as a high-risk factor.
3. Women or populations with low baseline dietary calcium intake (as defined by trial authors, or if not defined, mean intake of less than 900 mg per day)
4. Women or populations with adequate dietary calcium intake (as defined by trial authors, or if not defined, mean intake equal to or greater than 900 mg per day)

Types of interventions

1. High-dose supplementation ($\geq$ 1 g elemental calcium daily)

Supplementation with calcium from 34 weeks of pregnancy at the latest, compared with placebo treatment. We excluded studies with no placebo.

2. Low-dose supplementation (< 1 g elemental calcium daily)

Supplementation with calcium from 34 weeks of pregnancy at the latest, with or without cointerventions (e.g. vitamin D, linoleic acid, anti-oxidants or anti-platelet agents), compared with placebo or no treatment. We prespecified the inclusion criteria to be less restrictive than for the high-dose calcium comparisons because of the relatively small number of studies of low-dose calcium supplementation; we subgrouped the outcomes by the cointerventions. This was added in the 2013 revision of this review.

3. Comparison of different dosages of calcium, added in the 2018 revision of this review.

Types of outcome measures

In the original protocol we prespecified 15 clinical measures of maternal and fetal or neonatal morbidity and mortality. In October 2004 we added seven additional outcomes (marked * below). For the 2013 update we added two outcome measures, marked ** below, in order to include newly published data. As such, these should be regarded as post-hoc analyses, and interpreted with caution.

Primary outcomes

For the woman

1. High blood pressure as defined by trial authors, with or without proteinuria. Ideally, high blood pressure would be defined as diastolic blood pressure equal to or greater than 90 mmHg, or an increase in systolic blood pressure of 30 mmHg or more, or in diastolic blood pressure of 15 mmHg or more.
2. High blood pressure with significant proteinuria, as defined by trial authors. Ideally, proteinuria would be defined as 2+ by dipstick testing, equal to or greater than 300 mg per 24 hours, or equal to or greater than 500 mg per litre. Although the strict definition of pre-eclampsia includes confirmation of no hypertension or proteinuria outside pregnancy, for convenience the above definition is referred to in this review as **pre-eclampsia**.

For the child

1. Preterm birth (birth before 37 weeks of estimated gestation)
2. Admission to a neonatal intensive care unit
3. Stillbirth or death before discharge from hospital

Secondary outcomes

For the woman

1. Maternal death or serious morbidity. Serious morbidity includes eclampsia; renal failure; syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome); and admission to intensive care. This is a composite outcome of death or at least one measure of serious morbidity; in addition we planned to present each individual outcome.
2. Placental abruption
3. Caesarean section
4. *Proteinuria
5. *Severe pre-eclampsia as defined by trial authors
6. *Eclampsia
7. *HELLP syndrome
8. *Intensive care unit admission
9. *Maternal death
10. Mother's hospital stay of seven days or more
11. **Miscarriage

For the child

1. Low birthweight (the first weight obtained after birth less than 2500 g)
2. Neonate small-for-gestational age as defined by trial authors
3. Neonate in intensive care unit for seven days or more
4. *Death or severe neonatal morbidity
5. Childhood disability
6. Systolic blood pressure greater than 95th percentile during childhood
7. Diastolic blood pressure greater than 95th percentile during childhood
8. **Dental caries in childhood (one or more decayed, missing or filled teeth, or as defined by trial authors)

Only those outcomes with data appear in the analysis table.

Outcomes for 'Summary of findings' table

We included the following GRADE outcomes in the 'Summary of findings' table.

1. Pre-eclampsia
2. Preterm birth
3. HELLP syndrome

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (18 September 2017).

The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth in the Cochrane Library and select the 'Specialized Register' section from the options on the left side of the screen.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (18 September 2017) for unpublished, planned and ongoing trial reports using the terms given in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Hofmeyr 2014.

For this update, the following methods were used for assessing the reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager 5 software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

For each included study we assessed the method as being at:

1. low risk of bias (any truly random process, e.g. random number table; computer random number generator);
2. high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
3. unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For each included study we described the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as being at:

1. low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
2. high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
3. unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

For each included study we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as being at:

1. low, high or unclear risk of bias for participants;
2. low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

For each included study we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as being at:

1. low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses that we undertook.

We assessed methods as being at:

1. low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
2. high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
3. unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as being at:

1. low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
2. high risk of bias (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
3. unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

For each included study we described any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it was likely to have an impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses (Sensitivity analysis).

Assessment of the quality of the evidence using the GRADE approach

For this update we assessed the quality of the evidence using the GRADE approach, as outlined in the GRADE handbook, in order to assess the quality of the body of evidence relating to the following outcomes for our main comparison.

1. Pre-eclampsia
2. Preterm birth
3. HELLP syndrome

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014), in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. In future updates, as appropriate, we will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We have not identified any cluster-randomised trials to date. We will include any future cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify cluster-randomised trials in addition to the individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are not relevant to this review.

Other unit of analysis issues

For multiple-arm trials we have included only the two arms relevant to the review comparisons. We expect inclusion of multiple pregnancies to be rare. If multiple pregnancies are included in future updates of this review, we will analyse the neonates as individual participants. We will make adjustments for cluster effects only if the numbers of multiples are sufficient to justify statistical adjustment.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will use sensitivity analyses to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect.

For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30% and either Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by prespecified subgroup analysis.

Assessment of reporting biases

We investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using Review Manager 5 software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect, i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we planned not to combine trials. If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

High-dose calcium supplementation

We carried out the following subgroup analyses.

1. Trials in populations with low versus adequate dietary calcium intake
2. Trials in participants with low/average versus high hypertensive risk
3. Trials with small versus larger sample size
4. We also subgrouped the trials by both dietary calcium intake and trial size, to distinguish the differences between the two subgroups more clearly (not prespecified in the original protocol).

We used only primary outcomes in subgroup analyses 2, 3 and 4 above.

Low-dose calcium supplementation

We carried out subgroup analysis by cointerventions (comparison 6). This was not done for the high-dose calcium comparisons because cointerventions were not included.

We assessed subgroup differences by interaction tests available within Review Manager (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We carried out a planned sensitivity analyses to explore the effect of risk of bias assessed by concealment of allocation, high attrition rates, or both, with studies at high risk of bias being excluded from the analyses in order to assess whether this makes any difference to the overall result. This sensitivity analysis was only possible for the comparison of high-dose calcium versus placebo (there were too few studies in the comparison of low-dose calcium versus no supplementation).

R E S U L T S

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.

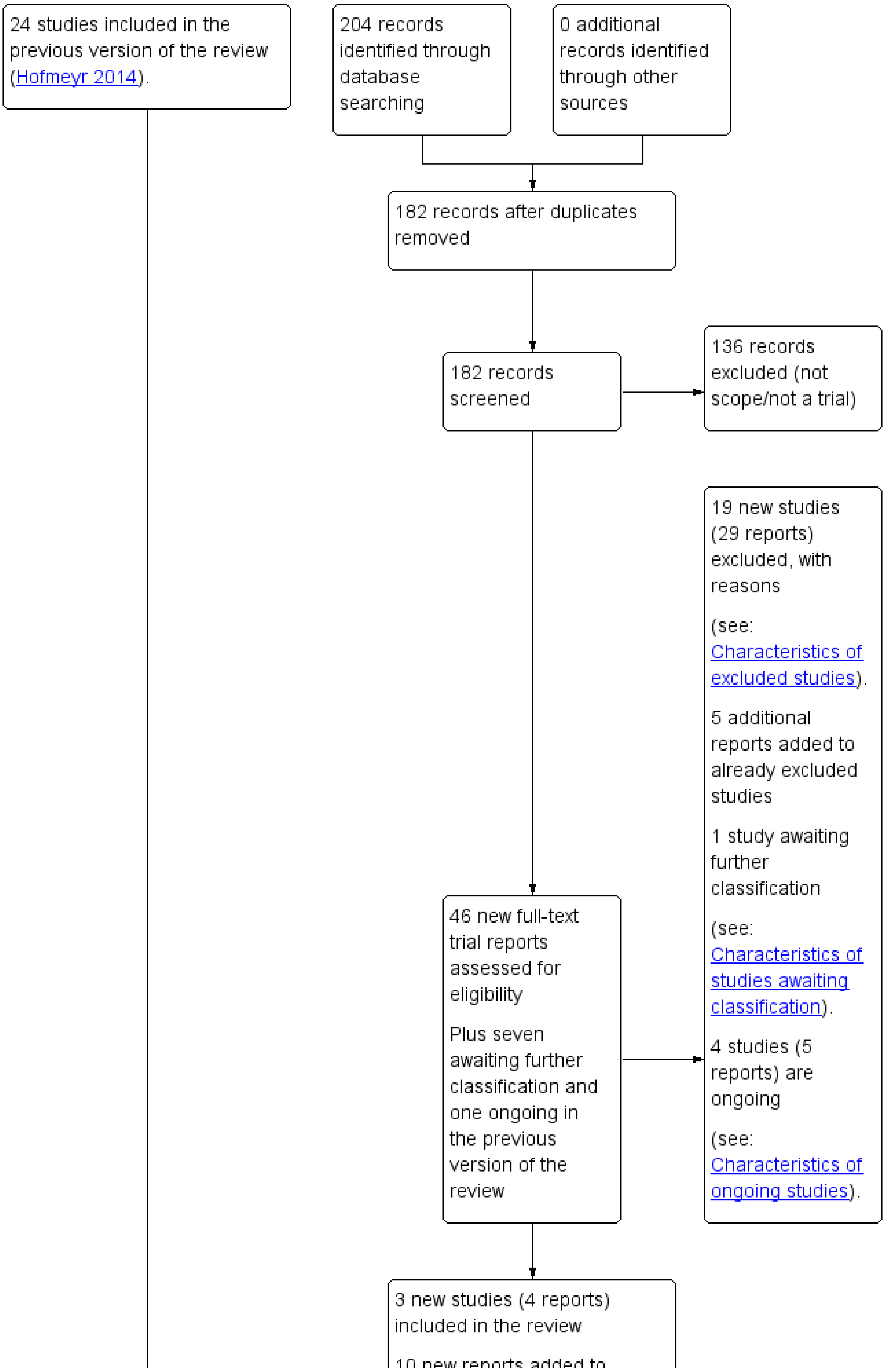
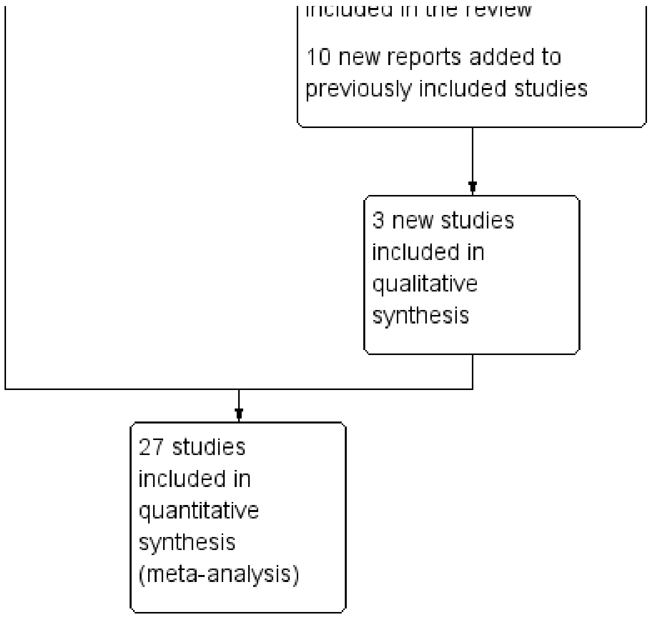


Figure 1. (Continued)



The 2017 search retrieved 46 reports; we also reassessed seven reports awaiting further classification and one ongoing study from the previous version of the review (Hofmeyr 2014). In this version of the review, one study is awaiting further assessment and there are now four ongoing studies (five reports). There were five additional reports relating to two studies already excluded from the review (Diogenes 2011; Ettinger 2011), and 10 additional reports relating to three studies already included in the review. We have included three new studies (four reports) in the review (Asemi 2012; Asemi 2016; Khan 2013) and have excluded a further 19 further studies (29 reports). In total, the review now includes 27 studies and 44 are excluded.

Included studies

The studies were carried out in countries across the world: Philippines (Almirante 1998); Iran (Asemi 2012; Asemi 2016; Niromanesh 2001; Taherian 2002); Trinidad (Bassaw 1998); Argentina (Belizan 1991); China (Cong 1995; Li 2000); Australia (Crowther 1999); Colombia (Herrera 1998); Gambia (Jarjou 2004); India (Khan 2013; Kumar 2009; Marya 1987; Purwar 1996); Ecuador (L-Jaramillo 1989; L-Jaramillo 1990; L-Jaramillo 1997); Hong Kong (Rogers 1999); Indonesia (Rumiris 2006); and the USA (CPEP 1997; S-Ramos 1994; Villar 1990). In addition there were multicentre studies carried out in more than one country (Herrera 2006; Villar 1987; WHO 2006).

In six of the studies the dates of recruitment were not clear or not stated (Almirante 1998; Cong 1995; CPEP 1997; L-Jaramillo 1990; Marya 1987; Niromanesh 2001). Recruitment started in the 1980s in five studies (Belizan 1991; L-Jaramillo 1989; S-Ramos 1994; Villar 1987; Villar 1990); in the 1990s in nine studies (Bassaw 1998; Crowther 1999; Herrera 1998; Jarjou 2004; Li 2000; L-Jaramillo 1997; Purwar 1996; Rogers 1999; Taherian 2002); and in the 2000s in seven studies (Asemi 2012; Asemi 2016; Herrera 2006; Khan 2013; Kumar 2009; Rumiris 2006; WHO 2006).

Many of these studies were conducted before it was required for sources of funding and conflict of interest declarations to be reported in published reports. Ten studies did not mention sources of funding. In two studies trial funding was not reported, but it was stated that study drugs were provided by pharmaceutical companies (Niromanesh 2001; Purwar 1996); pharmaceutical companies also provided drugs for other trials that were otherwise government, health service or university funded (Asemi 2012; Asemi 2016; CPEP 1997; Jarjou 2004). Other trialists also stated that studies were supported by university, government or hospital funding (Crowther 1999; Herrera 1998; Herrera 2006; Jarjou 2004; Kumar 2009; L-Jaramillo 1989; Taherian 2002). Two studies were WHO funded (L-Jaramillo 1997; WHO 2006) and two were funded by national dairy food organisations (Villar 1987; Villar 1990).

Only two of the studies explicitly stated that authors had no known conflict of interest (Asemi 2016; Jarjou 2004).

Compliance, where reported, was generally more than 80% (84% and 86% for calcium and placebo in Belizan 1991; 84.5% and 86.2% in WHO 2006; 79% and 81% in S-Ramos 1994). However, in one study compliance was 64% and 67% in the respective groups (CPEP 1997), and in another, 31% and 24% of women from each group stopped taking the tablets before the end of the trial (Crowther 1999). In L-Jaramillo 1997, two women were withdrawn for non-compliance.

High-dose calcium supplementation (1 g/day or more)

We included 14 studies examining high-dose supplements in the review. One study contributed no data, although authors have been contacted and data may be available for the next update (Jarjou 2004). Of the remaining 13 studies, four were multicentre studies: one was conducted in Argentina (Belizan 1991), one in the USA (CPEP 1997), another in Australia (Crowther 1999), and the fourth was international (WHO 2006). Most of the 15,730 women recruited to these studies were low risk (15,143 women) and had a low dietary intake of calcium (10,678). Most studies only recruited women who were nulliparous or primiparous. One study did not state the parity of women recruited (Niromanesh 2001), and another commented that most women were nulliparous (Villar 1990). For most studies the intervention was 1.5 g to 2 g per day of calcium. All of these studies compared high-dose supplementation with a placebo.

Five studies enrolled women considered to be at high risk of pre-eclampsia. The definitions of high risk and the actual risk (rate of pre-eclampsia in the placebo group) were variable: positive 'roll-over' test at 28 to 30 weeks (8/34) (L-Jaramillo 1990); teenagers 17 years or younger (3/88) (Villar 1990); positive 'roll-over' test at 28 to 32 weeks plus one clinical risk factor (7/15) (Niromanesh 2001); positive 'roll-over' and positive angiotensin II infusion test (15/34) (S-Ramos 1994); and nulliparous teenagers 17.5 years or younger (21/135) (L-Jaramillo 1997). The clinical usefulness of the pooled results in this subgroup is therefore limited.

Two included studies conducted long-term follow-up of the children whose mothers were recruited to these trials (Belizan 1991; Hiller 2007). In Belizan 1991, only the subset of women recruited in private clinics were contacted; and in Hiller 2007, the outcomes reported differed from this review (but unpublished data may be made available by the authors at a later date).

Other studies have reported outcomes for small subsets of women (CPEP 1997: Hatton 2003; WHO 2006: Zhang 2007), but these data did not meet the inclusion criteria for this review.

Low-dose calcium supplementation (less than 1 g/day)

We included 12 studies: four investigated calcium supplementation alone (Almirante 1998; Bassaw 1998; Cong 1995; Rogers 1999); five investigated calcium plus vitamin D (Asemi 2012; Asemi 2016; Li 2000; Marya 1987; Taherian 2002); two studies from the same group investigated calcium plus linoleic acid (Herrera 1998; Herrera 2006); and one investigated calcium plus antioxidants (Rumiris 2006).

Comparisons varied in the studies: five used placebo (Asemi 2012; Asemi 2016; Herrera 1998; Herrera 2006; Rumiris 2006); one used aspirin tablets (Bassaw 1998); four compared with no treatment (Cong 1995; Li 2000; Marya 1987; Taherian 2002); and two did not clearly describe their control group (Almirante 1998; Rogers 1999).

High-dose versus low-dose calcium supplementation (1 g/day or more versus less than 1 g/day)

One study compared high-dose (2 g) with low-dose (500 mg) calcium supplementation in unselected, normotensive pregnant women from a low socio-economic status population in West Begal, India, from 34 weeks of pregnancy at the latest (Khan 2013) . A discrepancy between the numbers in each group was not accounted for, and we assessed the risk of bias as unclear.

Please see Characteristics of included studies for further details.

Excluded studies

We excluded 44 studies from the review (Characteristics of excluded studies).

There were a number of reasons for exclusion, and we excluded some studies for more than one reason. In five studies it was not clear how participants were allocated to groups and in some cases the method of allocation was non-random (Felix 1991; Karandish 2003; Kawasaki 1985; Raman 1978; Salzano 2001). We excluded two other studies because of methodological problems; either the specified outcomes were not reported (Boggess 1997), or there were unexplained group discrepancies (Dizavandy 1998). In seven studies, reported in abstracts, there was too little information on methods and results for us to judge risk of bias and include data (Aghamohammady 2010; August 2002; Belizan 1983; Chames 2002; Prada 2001; Prada 2002; Repke 1989). There were four studies reported in trial registrations where it was not clear that studies had started or been completed (Anumba 2006; Bhatia 2010; Fung 2010; Lavin 1986). In one study the intervention was not calcium but rather dairy foods (Chan 2006), and in eight studies the intervention was not calcium alone but rather calcium plus other vitamins and minerals which could not be meaningfully included (Asemi 2017; Azami 2017 (unclear trial procedures); de Souza 2006 (high-dose calcium plus aspirin); Diogenes 2011 (no hypertension data); MacDonald 1986 (no methods or results); Mosalanejad 2016 (calcium in both groups, vitamin D dose varied); Nooripour 2016 (calcium in both groups, vitamin D varied); Souza 2014 (high-dose calcium plus aspirin)). In seven studies there was no placebo and calcium may have been compared with other active interventions (Anu 2017; Knight 1992; Montanaro 1990; Subprabha 2017; Suzuki 1996; Wanchu 2001; Zheng 2000). In three studies the aim of the intervention did not relate to maternal hypertension (Ettinger 2011; Herrera 2006a; Karamali 2016), and in a further three the participants were not eligible (e.g. they already had hypertension at recruitment) (NCT00000543; S-Ramos 1995; Tamas 1997). In Hofmeyr 2015, women were not pregnant at the time of recruitment. One study was a dose comparison (Martin 2017), one examined high-dose calcium (1 g) with vitamin D (Samimi 2016), and another examined the effects of enteric coating of calcium supplements on absorption (Roth 2014).

Risk of bias in included studies

See Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

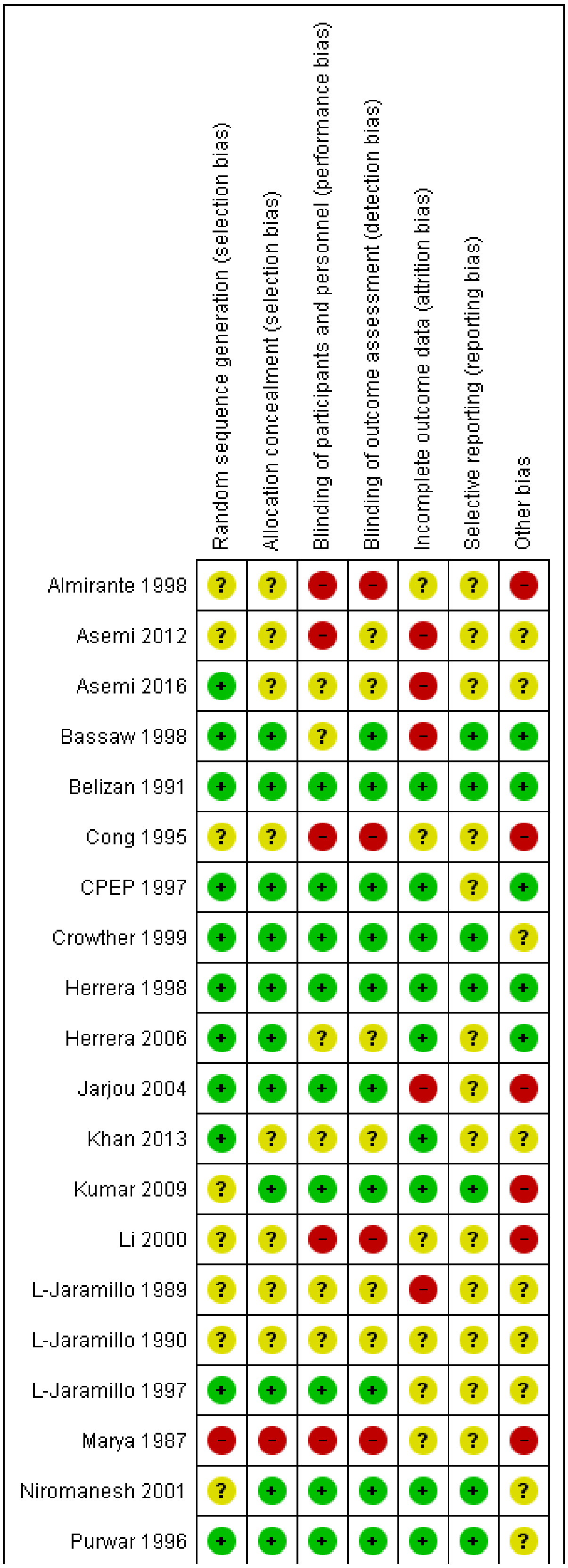


Figure 2. (Continued)

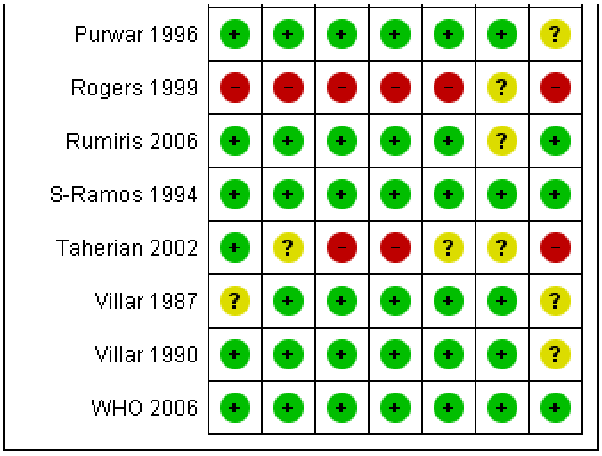
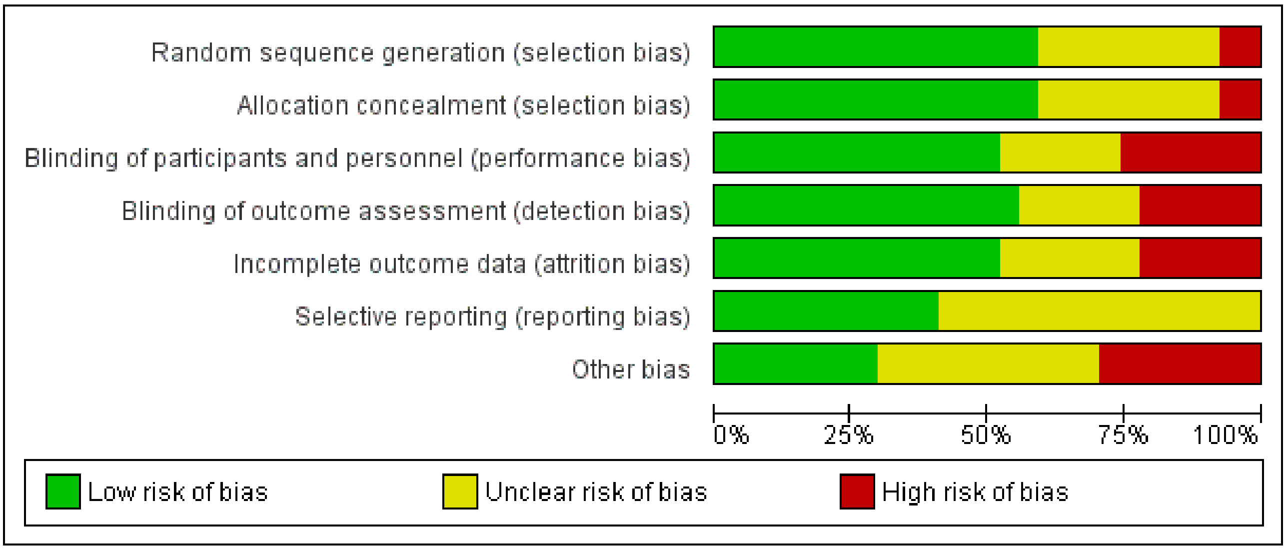


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

The majority of studies included in the review used methods of sequence generation and allocation that we assessed as having low risk of bias. Sixteen trials used random number tables, computer generation or central randomisation methods to generate the randomisation sequence. Nine trials did not provide clear information about how the sequence was generated and two studies used methods that we assessed as being at high risk of bias (Marya 1987; Rogers 1999). The methods to conceal allocation at the point of randomisation were assessed as having low risk of bias in 16 trials, unclear risk of bias in nine trials, and high risk of bias in two trials.

Blinding

Where trials were placebo controlled, and it was clear that women and staff providing care were blind to treatment allocation, we assessed the studies as having low risk of performance bias; this applied to 14 trials. In six trials the methods to achieve blinding were not clearly described, and we assessed seven trials to have high risk of performance bias as women or staff were aware of the treatment group. For detection bias, we assessed 15 studies to have low risk of bias, six to have unclear risk of bias, and six to be at high risk of bias.

Incomplete outcome data

In six studies there were post-randomisation exclusions or loss to follow-up that meant we considered the studies to be at high risk of attrition bias. In seven studies, sample loss was either not described or we were uncertain about the impact of loss to follow-up on results. In the remaining 14 trials, loss to follow-up was low and balanced across groups and so we assessed these studies as being at low risk of bias.

Selective reporting

For 16 trials we had insufficient information to assess risk of outcome reporting bias; many trials did not have published protocols or did not report expected outcomes fully. We assessed 11 trials as being at low risk of outcome reporting bias.

Other potential sources of bias

We assessed eight trials as being at high risk of other bias, mainly because the methods were very poorly described. We assessed another eight trials as being unlikely to be at high risk of other bias; and for 11 studies we were uncertain, again often because of limited reporting.

Overall risk of bias in our main comparisons

High-dose calcium supplementation

For overall risk of bias, all were double-blind, placebo-controlled trials. Pre-specified outcome data were not available from all trials. Not all outcomes were consistently reported, therefore there is a possibility of reporting bias in some trials.

In L-Jaramillo 1990, a large discrepancy in numbers allocated to each group was not explained. For Kumar 2009, we contacted the authors to clarify the imbalance in group size that occurred in their study. They have provided the explanation (see notes in Characteristics of included studies), but the imbalance does increase the potential for bias.

In some trials, individual denominators were not given for specific outcomes. Where it was clear that the outcomes were not measured in the entire group, we have adjusted the denominators accordingly. In other respects, the methodology of the studies included appears sound.

Low-dose calcium supplementation

We considered four of these studies to be at low risk of bias (Bassaw 1998; Herrera 1998; Herrera 2006; Rumiris 2006), and six to be at high risk of bias because no placebo was used and either because random sequence generation and allocation concealment were not reported (Almirante 1998; Cong 1995; Li 2000); a consecutive series was used (Marya 1987); an open envelope method was used (Rogers 1999); or a 'table of random numbers' was reported to be used but there was no report of allocation concealment (Taherian 2002).

Effects of interventions

See: **Summary of findings for the main comparison**

High-dose calcium supplementation versus placebo

In the 13 studies included in the meta-analysis, significant heterogeneity of results occurred for four outcomes: pre-eclampsia; high blood pressure; preterm birth and birthweight less than 2500 g. Factors accounting for the heterogeneity appeared to be maternal risk at trial entry, dietary calcium and trial size. The small trials have bigger effect sizes than the large trials; but as all the small trials recruited high-risk women, this could also be related to risk status. In view of the heterogeneity, we used a random-effects model for these four outcomes. As part of our sensitivity analysis, we removed the data from a study assessed to be at high risk of attrition bias (L-Jaramillo 1989).

Data were not available for the following secondary outcomes: mother's hospital stay seven days or more; miscarriage; neonate in intensive care unit seven days or more; death or severe neonatal morbidity; and childhood disability.

Primary outcomes

(1) High blood pressure with or without proteinuria

The results follow a similar pattern to those for pre-eclampsia (see below). Overall, there were fewer women with high blood pressure with calcium supplementation compared with placebo (12 trials, 15,470 women: average risk ratio (RR) 0.65, 95% confidence interval (CI) 0.53 to 0.81; heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 42.40$, df = 11, $P < 0.0001$; $I^2 = 74\%$; Analysis 1.1). The reduction in RR was greatest for the small trials, i.e. trials with fewer than 400 women (seven trials, 675 women: average RR 0.38, 95% CI 0.21 to 0.68; heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 18.26$, df = 6, P = 0.006; $I^2 = 67\%$; test for subgroup differences: $Chi^2 = 6.20$, df = 1 (P = 0.01), $I^2 = 83.9\%$; Analysis 3.1.1), and for those with low baseline dietary calcium (seven trials, 10,418 women: average RR 0.44, 95% CI 0.28 to 0.70; heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 39.35$, df = 6; test for subgroup differences: $Chi^2 = 8.78$, df = 2 (P = 0.01), $I^2 = 77.2\%$; Analysis 1.1.2). Asymmetric funnel plots for these analyses suggest that the treatment effect may be overestimated due to small-study effects or publication bias (Figure 4, Figure 5, Figure 6).

Figure 4. Funnel plot of comparison: 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, outcome: 2.1 High blood pressure (with or without proteinuria).

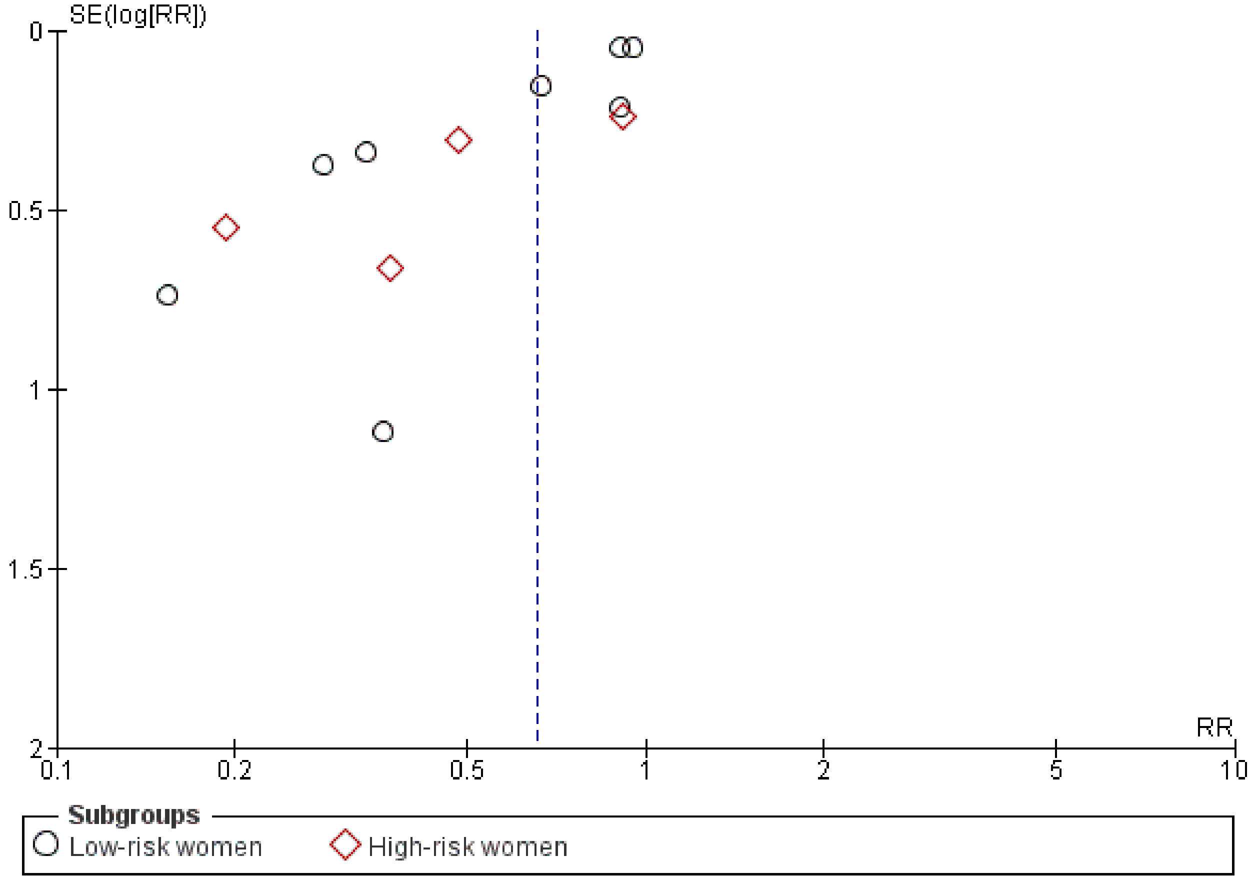


Figure 5. Funnel plot of comparison: 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, outcome: 1.1 High blood pressure (with or without proteinuria).

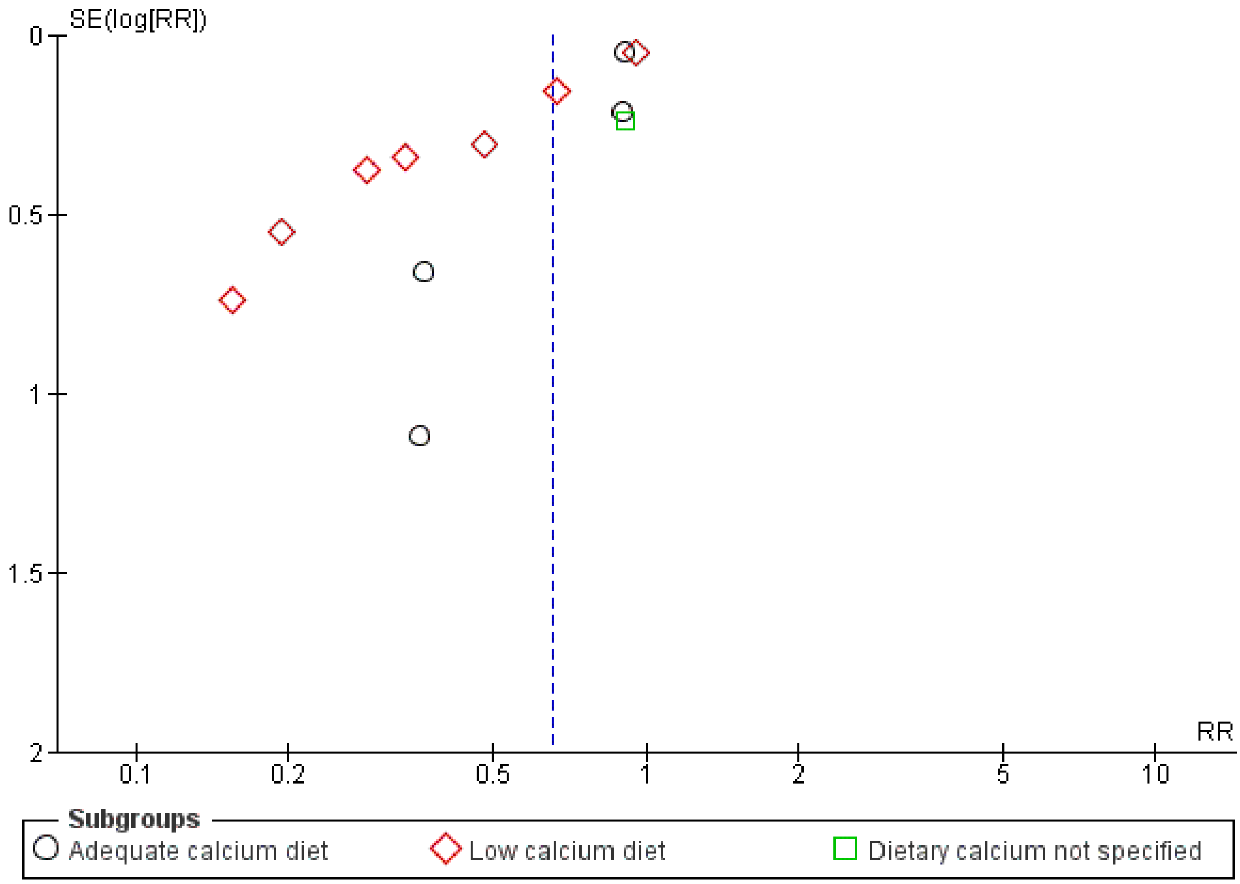
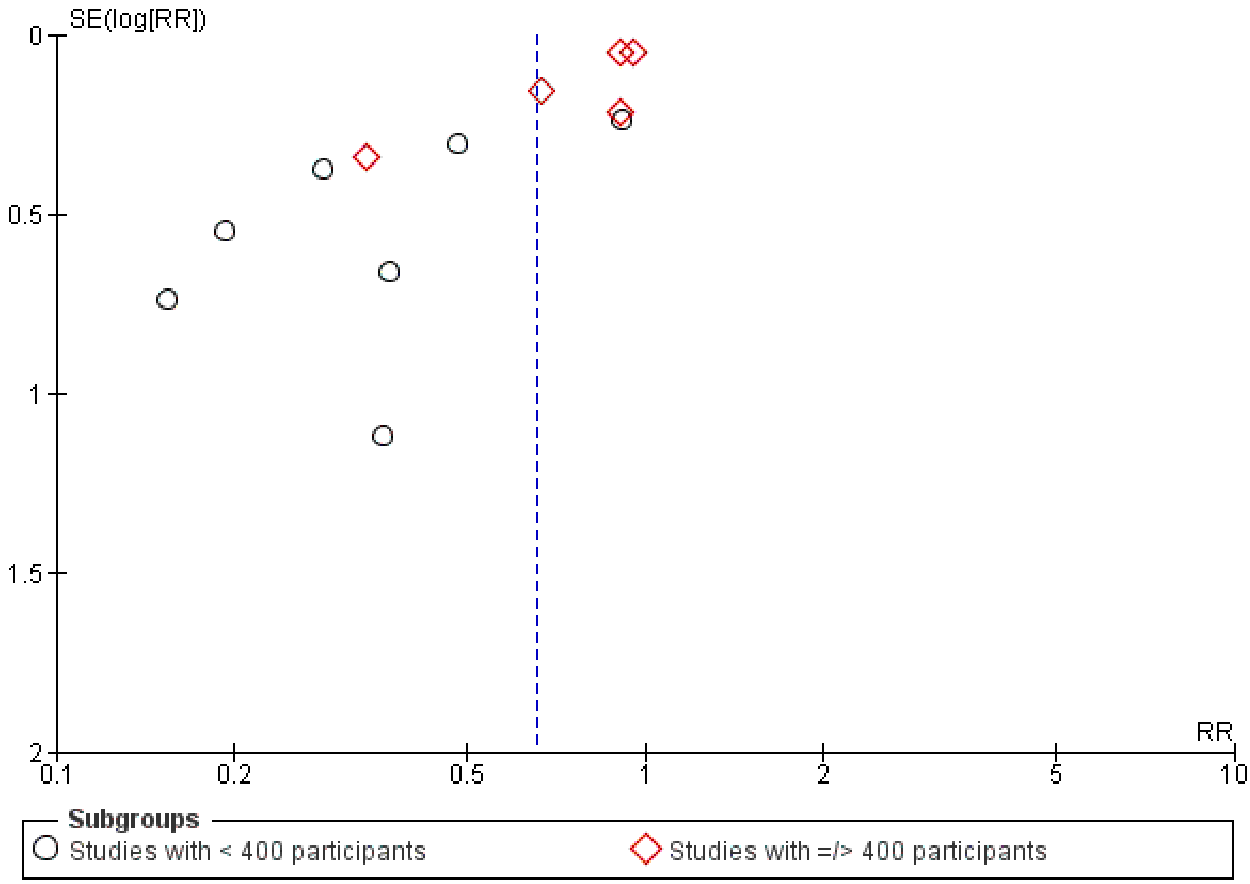


Figure 6. Funnel plot of comparison: 3 Routine high-dose calcium supplementation in pregnancy by study sample size, outcome: 3.1 High blood pressure (with or without proteinuria).



(2) Pre-eclampsia

Overall, there was a reduction in the average risk of pre-eclampsia (13 trials, 15,730 women: RR 0.45, 95% CI 0.31 to 0.65, low-quality evidence; heterogeneity: Tau² = 0.20; Chi² = 40.31, df = 12 (P < 0.0001; I² = 70%); Analysis 1.2. This reduction in RR was greatest for women at high risk of pre-eclampsia (five trials, 587 women: average RR 0.22, 95% CI 0.12 to 0.42; test for subgroup differences: Chi² = 6.81, df = 1, P = 0.009, I² = 85.3%; Analysis 2.2). Pre-eclampsia was not reduced in the subgroup with adequate dietary calcium, but was for those with low baseline calcium intake (eight trials, 10,678 women: average RR 0.36, 95% CI 0.20 to 0.65; heterogeneity: Tau² = 0.44; Chi² = 29.35, df = 7, P = 0.0001; I² = 76%; Analysis 1.2). Assymetric funnel plots for these analyses suggest that the treatment effect may be overestimated due to small-study effects or publication bias (Figure 7, Figure 8). There was also evidence of a subgroup difference between studies with small and larger samples sizes (test for subgroup differences: Chi² = 15.20, df = 1 (P < 0.0001), I² = 93.4%), Analysis 3.2.

Figure 7. Funnel plot of comparison: 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, outcome: 1.2 Pre-eclampsia.

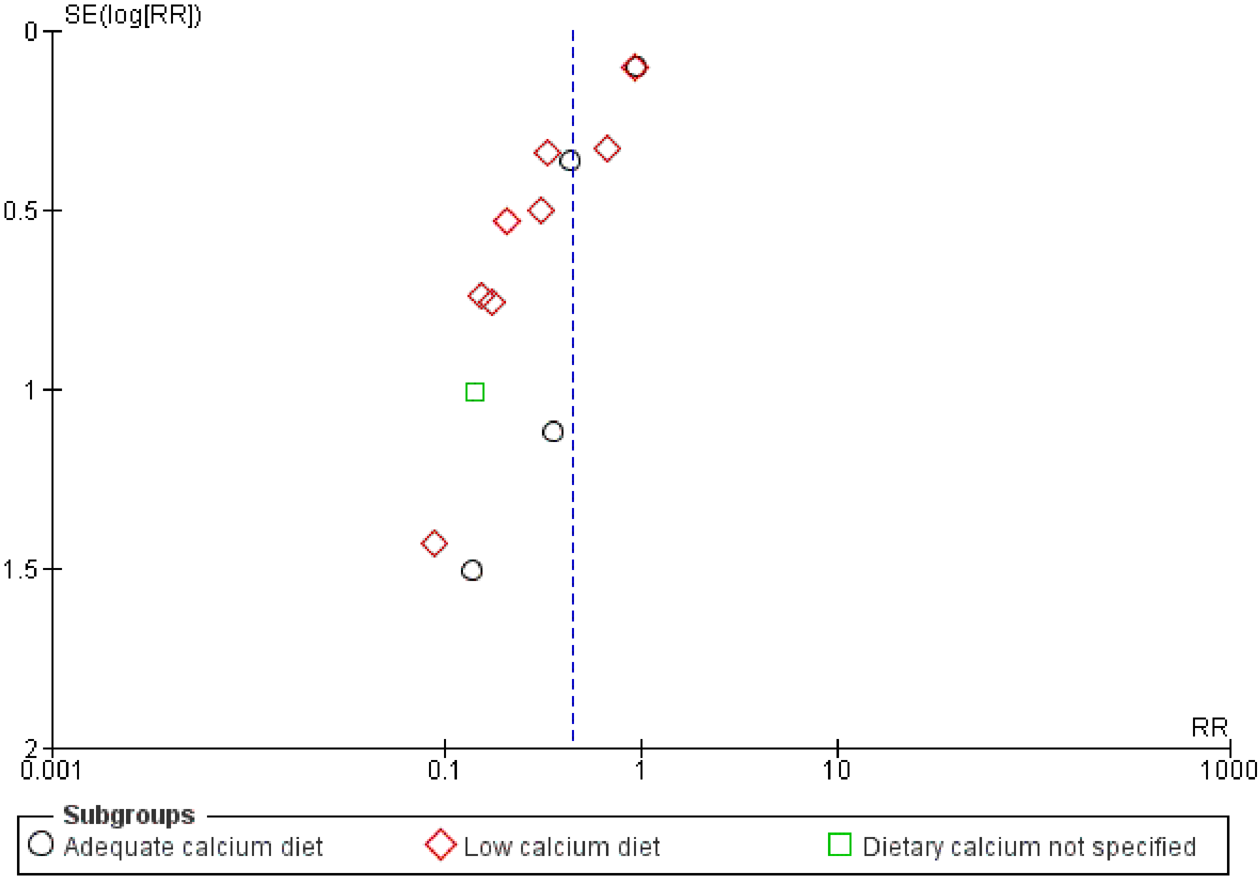
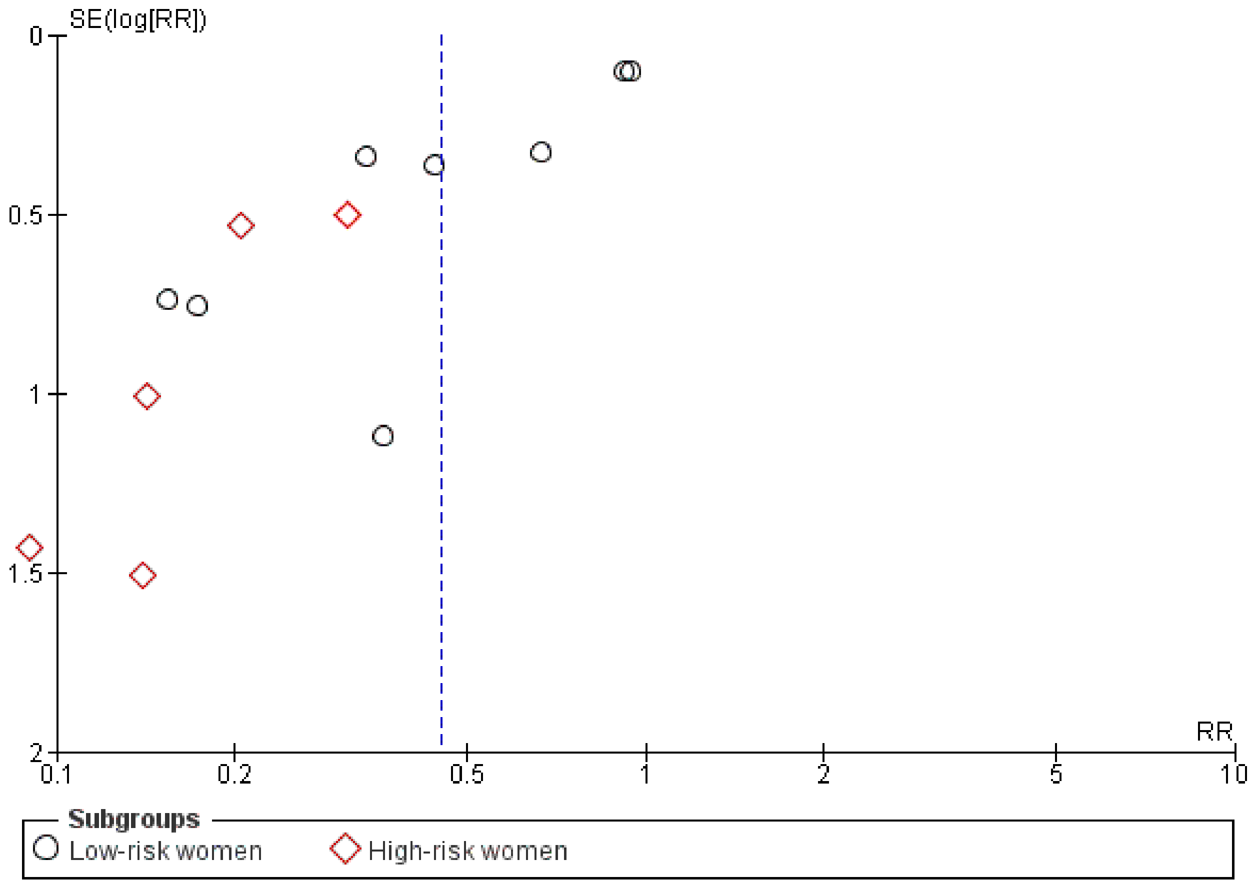
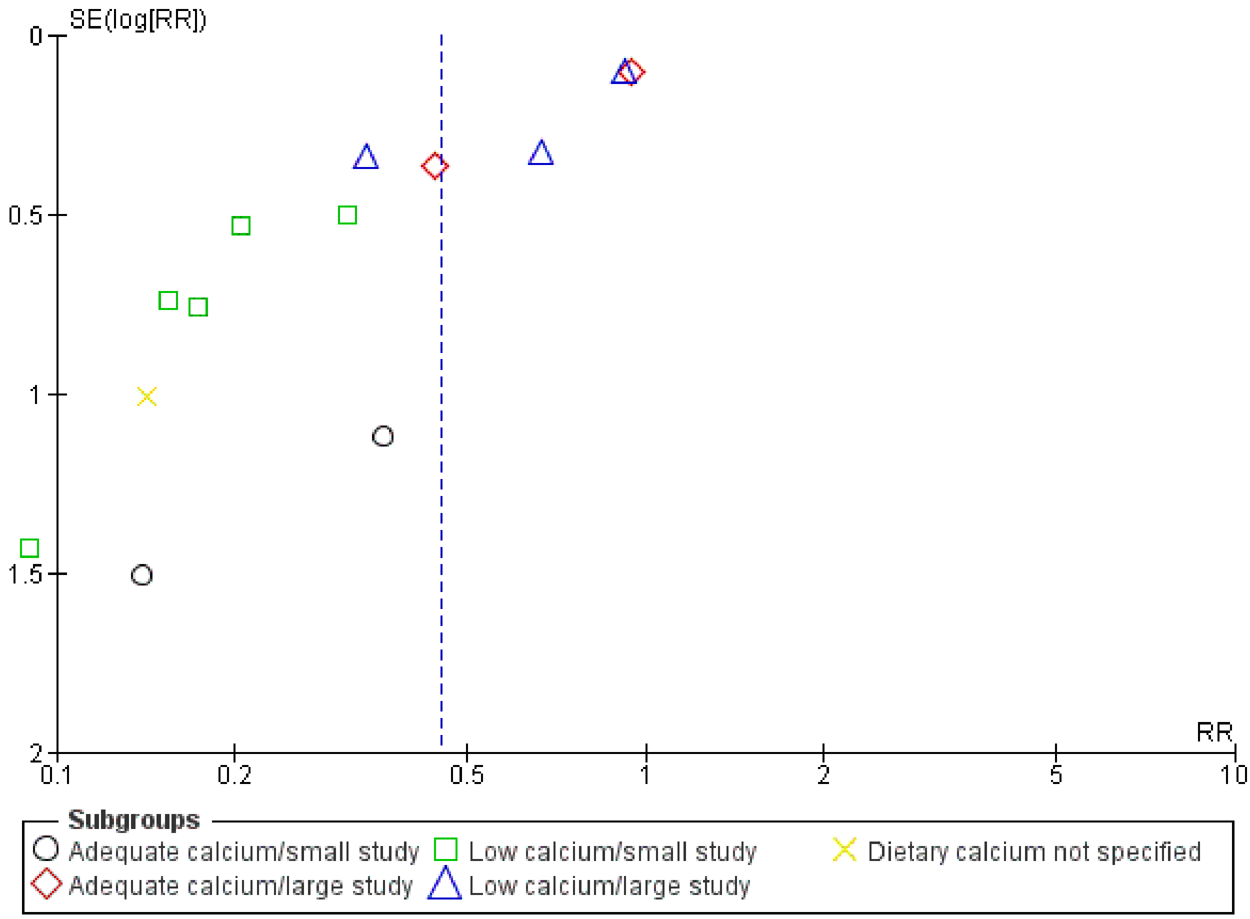


Figure 8. Funnel plot of comparison: 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, outcome: 2.2 Pre-eclampsia.



When subgrouped by both dietary calcium intake and study size, the effect size appeared to be associated most strongly with study size (in the small studies, RR 0.21 for the low-calcium trials and RR 0.26 for the adequate-calcium trials; and in the large studies RR 0.63 and RR 0.70 respectively; Analysis 4.1; test for subgroup differences: $Chi^2 = 10.28$, df = 4 (P = 0.04), $I^2 = 61.1\%$); Figure 9.

Figure 9. Funnel plot of comparison: 4 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium and study sample size (not pre-specified), outcome: 4.1 Pre-eclampsia.



Only one study included women with high risk of pre-eclampsia and adequate dietary calcium (Villar 1990). The numbers were too small for meaningful statistical analysis (pre-eclampsia in 0/90 participants with calcium, versus 3/88 participants with placebo).

(3) Preterm birth

Calcium supplementation reduced the average risk of preterm birth overall (11 trials 15,275 women: RR 0.76, 95% CI 0.60 to 0.97; low-quality evidence; heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 20.04$, df = 8 (P = 0.01); $I^2 = 60\%$; Analysis 1.3), and amongst women at high risk of developing pre-eclampsia recruited to four small trials (568 women: average RR 0.45, 95% CI 0.24 to 0.83; heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.73$, df = 2, P = 0.42; $I^2 = 0\%$; test for subgroup differences: $Chi^2 = 3.48$, df = 1 (P = 0.06), $I^2 = 71.3\%$; Analysis 2.3). However, this reduction did not translate to a reduction in neonatal high care admissions of babies born < 2500 g. Asymmetric funnel plots for these analyses suggest that the treatment effect may be overestimated due to small-study effects or publication bias (Figure 10, Figure 11, Figure 12). There was also evidence of a subgroup difference between studies with small and larger samples sizes (test for subgroup differences: $Chi^2 = 4.90$, df = 1 (P = 0.03), $I^2 = 79.6\%$, Analysis 3.3).

Figure 10. Funnel plot of comparison: 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, outcome: 1.3 Preterm birth.

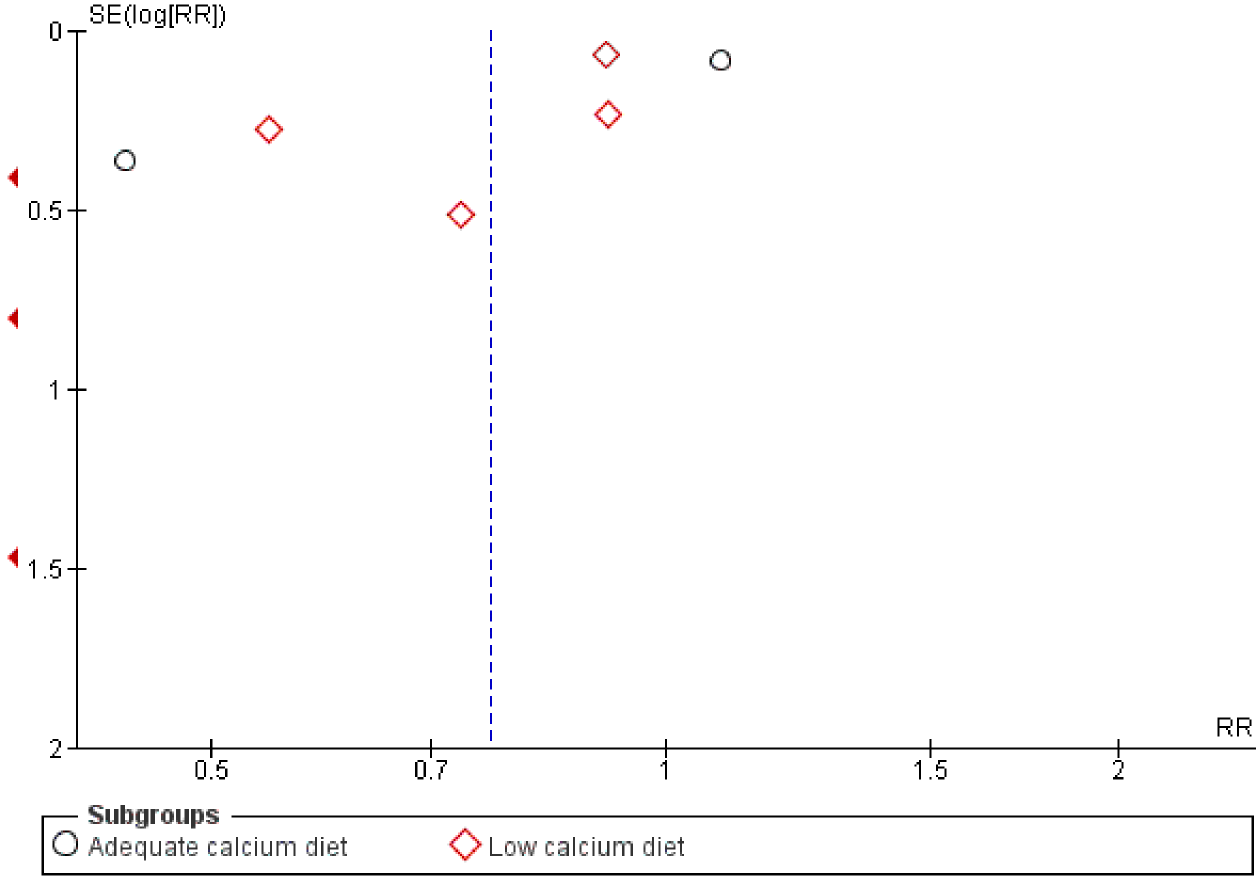


Figure 11. Funnel plot of comparison: 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, outcome: 2.3 Preterm birth.

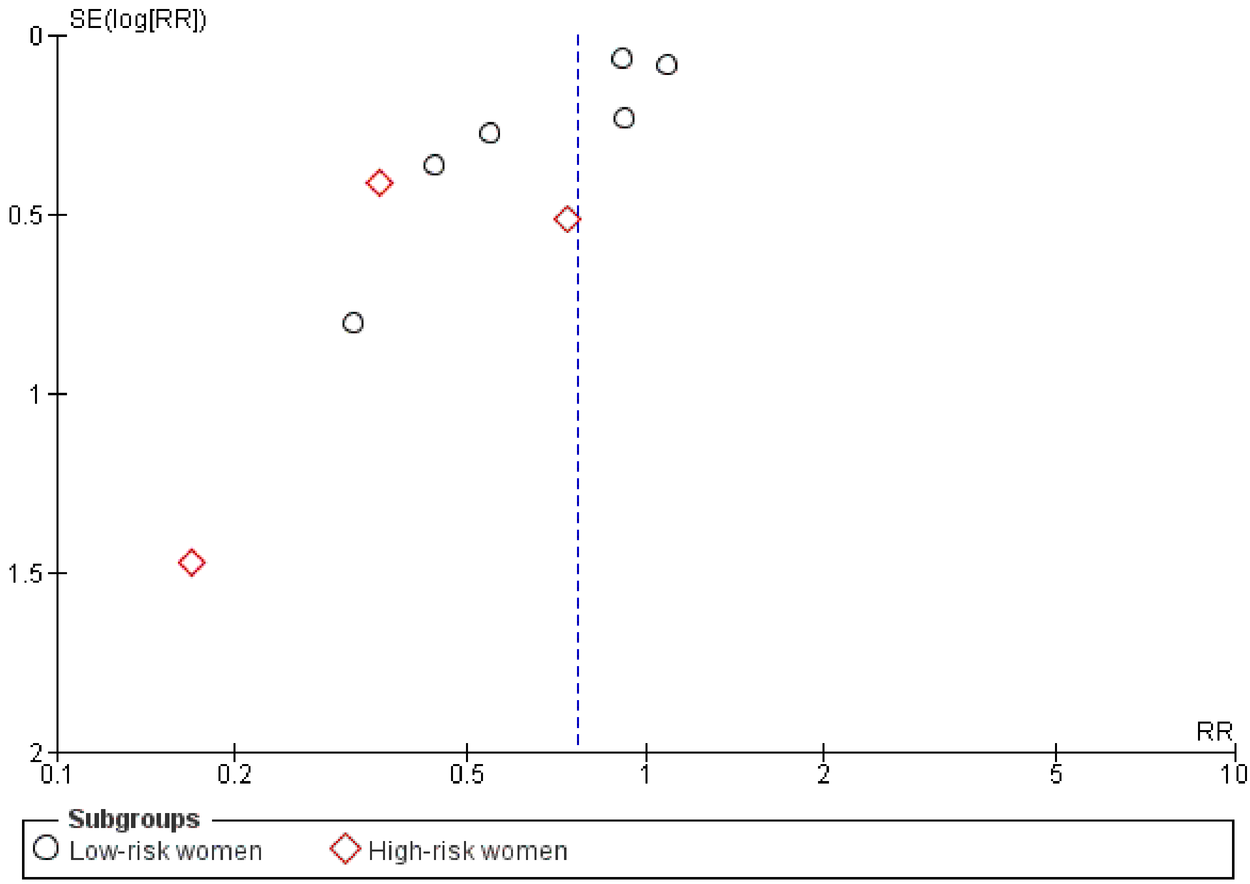
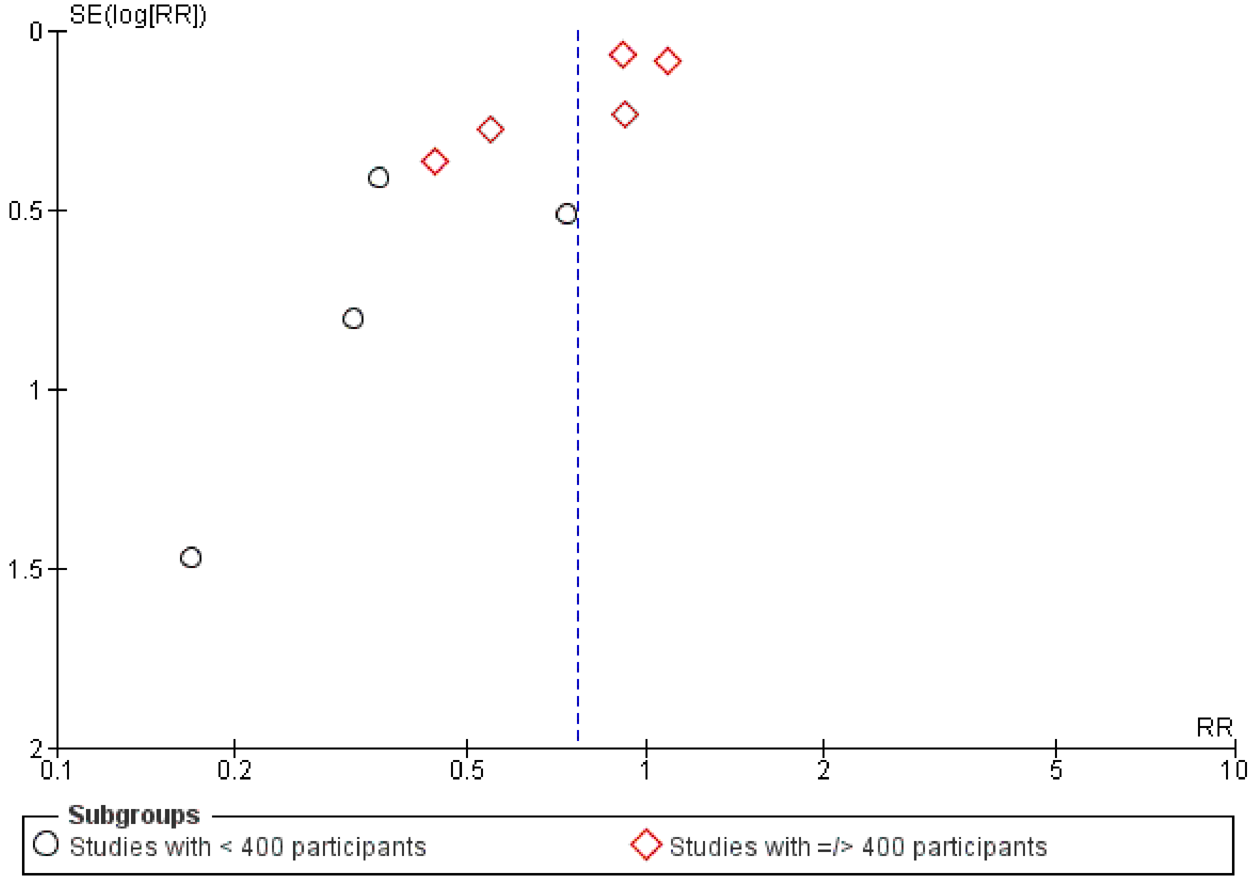


Figure 12. Funnel plot of comparison: 3 Routine high-dose calcium supplementation in pregnancy by study sample size, outcome: 3.3 Preterm birth.



(4) Admission to neonatal intensive care unit

There was no overall effect on the RR of admission to a neonatal intensive care unit (four trials, 13,406 women: RR 1.05, 95% CI 0.94 to 1.18; heterogeneity: $Chi^2 = 2.83$, df = 3 (P = 0.42); $I^2 = 0\%$; Analysis 1.4).

(5) Stillbirth or death before discharge from hospital

There was no overall effect on the RR of a stillbirth or the baby dying before discharge from hospital (11 trials, 15,665 women: RR 0.90, 95% CI 0.74 to 1.09; heterogeneity: $Chi^2 = 1.46$, df = 5 (P = 0.92); $I^2 = 0\%$; Analysis 1.5).

Secondary outcomes

(6) Maternal death or serious morbidity

The risk of maternal death or serious morbidity was reduced for women allocated to calcium supplementation compared with placebo (four trials, 9732 women: RR 0.80, 95% CI 0.66 to 0.98; Analysis 1.6). It should be noted that all events were restricted to one trial (WHO 2006) as the other three trials did not have any events.

(7) Placental abruption

In the five trials reporting this outcome, there was no clear difference between the groups (14,336 women: RR 0.86, 95% CI 0.55 to 1.34; heterogeneity: $Chi^2 = 0.91$, df = 2 (P = 0.63); $I^2 = 0\%$; Analysis 1.7).

(8) Caesarean section

There was a reduction in caesarean section for women in the calcium group (eight trials, 15,234 women: RR 0.95, 95% CI 0.89 to 1.02; heterogeneity: $Chi^2 = 5.21$, df = 7 (P = 0.63); $I^2 = 0\%$; Analysis 1.8), although the upper confidence limit just crossed the line of no effect.

(9) *Proteinuria

Only one trial reported proteinuria (WHO 2006), and there was no overall difference between the groups (8312 women: RR 1.04, 95% CI 0.86 to 1.26; Analysis 1.9).

(10) *Severe pre-eclampsia as defined by trial authors

Only one trial reported severe pre-eclampsia (WHO 2006). Again, there was no clear difference between the groups (one trial, 8302 women: RR 0.74, 95% CI 0.48 to 1.15; Analysis 1.10).

(11) *Eclampsia

The two largest trials reported eclampsia (CPEP 1997; WHO 2006), as well as Kumar 2009. There was no clear difference between the groups (three trials, 13,425 women: RR 0.73, 95% CI 0.41 to 1.27; Analysis 1.11).

(12) *HELLP syndrome

Only the two largest studies reported HELLP syndrome (CPEP 1997; WHO 2006). The RR was higher for women allocated calcium supplementation, compared with placebo (two trials, 12,901 women: RR 2.67, 95% CI 1.05 to 6.82; high-quality evidence; heterogeneity: $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0\%$; Analysis 1.12).

(13) *Maternal intensive care unit admission

Only one trial reported admission to intensive care (WHO 2006). There was no clear difference between the groups (one trial, 8312 women: RR 0.84, 95% CI 0.66 to 1.07; Analysis 1.13).

(14) *Maternal death

Only one trial reported maternal deaths (WHO 2006). There were few events in any group, with only one death in the calcium group and six in the placebo group (one trial, 8312 women: RR 0.17, 95% CI 0.02 to 1.39; Analysis 1.14).

(15) Low birthweight (birthweight less than 2500 g)

Women in the calcium group were at reduced risk of having a baby with birthweight less than 2500 g (nine trials, 14,883 women: average RR 0.85, 95% CI 0.72 to 1.01; heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.93$, df = 5 (P = 0.08); $I^2 = 50\%$; Analysis 1.15), although the overall effect estimate just crossed the line of no effect.

(16) Neonate small-for-gestational age

There was no overall effect on the RR of the baby being born small-for-gestational age (four trials, 13,615 women: RR 1.05, 95% CI 0.86 to 1.29; heterogeneity: $Chi^2 = 2.74$, df = 3 (P = 0.43); $I^2 = 0\%$; Analysis 1.16).

(17) Childhood systolic blood pressure > 95th percentile

One trial assessed during childhood a subset of the children recruited whilst in utero (Belizan 1991). At about seven years of age, diastolic blood pressure greater than 95th percentile was reduced (514 women: RR 0.59, 95% CI 0.39 to 0.91; Analysis 1.17). While the baseline calcium intake in the original study was low (mean 646 mg, standard deviation (SD) 396 in the calcium group; and mean 642 mg, SD 448 in the placebo group, in a sample assessed during the first four months of the study), the group followed up were only from among the 614 women from the private hospital, not the 580 from the public hospitals. Their dietary calcium intake may have differed from the mean (i.e. it is more likely to be higher in more affluent women). The baseline calcium status of the women in this part of the study therefore cannot be classified.

In Crowther 1999, a follow-up of mothers and offspring was conducted four to seven years later (45% of the original participants) and reported in Hiller 2007. Childhood blood pressure was reported as a continuous variable. It was concluded that calcium supplementation during pregnancy may lower the mean blood pressure of the children of women with hypertension in pregnancy. We have sought additional unpublished data from the authors which may be available/suitable for inclusion in the next update.

A limited follow-up of mothers and infants from CPEP 1997, found reduced systolic blood pressure at two years of age in the calcium supplementation group (mean 95.4 mmHg, SD 7.6, n = 35 versus 100.2, 7.9, n = 18). We have not included the data in this review because the low and unequal follow-up rate (35 and 18 from 497 invited to participate) limits the reliability of the results. In another report of CPEP 1997 (Hatton 2003), reduced systolic blood pressure was found in the offspring of the calcium supplementation group at two years of age. We have not included these data either because of the high losses to follow-up.

A subsequent report of the Gambian trial (Jarjou 2004) found no significant difference in systolic blood pressure in 64% of the original trial offspring at between five and 10 years of age. This analysis was restricted to children born at term and the relevant data were not available for our meta-analysis.

(18) Childhood diastolic blood pressure > 95th percentile

Data were available only from one study (Belizan 1991). There was no difference between groups (Analysis 1.18).

(19) Dental caries in childhood

In one study (Belizan 1991), dental caries was assessed at 12 years of age in a subset of those enrolled. It is was not specified how this subset was randomly selected. As this was a post hoc outcome for this review, the data should be interpreted with caution. The study found a significant reduction in dental caries, defined as at least one decayed, filled or missing tooth (one trial, 195 children: RR 0.73, 95% CI 0.62 to 0.87; Analysis 1.19).

(20) Non-prespecified outcomes (comparison 5)

Sub-studies of WHO 2006 found no effect of calcium supplementation on uterine or umbilical artery resistance index or ultrasound estimates of fetal growth at 32 weeks; or platelet count, uric acid or urine protein/creatinine ratio at 35 weeks.

Sensitivity analysis

One study contributing data to this analysis was assessed to be at high risk of attrition bias (L-Jaramillo 1989). Removing these study data from the analyses for high blood pressure (with or without proteinuria) (Analysis 1.1; Analysis 2.1; Analysis 3.1); pre-eclampsia (Analysis 1.2; Analysis 2.2; Analysis 3.2; Analysis 4.1); stillbirth or death before discharge from hospital (Analysis 1.5; Analysis 2.5; Analysis 3.5); and low birthweight (Analysis 1.15) made little or no difference to the overall effect estimates.

Low-dose calcium supplementation with or without cointerventions, versus no calcium supplementation

We included nine studies with 2234 participants. The risk of bias was variable, and studies included those with and without co-interventions.

Data were not available for the following secondary outcomes: maternal death or serious morbidity; proteinuria; HELLP syndrome; intensive care unit admission; mother's hospital stay seven days or more: neonate in intensive care unit seven days or more; death or severe neonatal morbidity; childhood disability; systolic blood pressure greater than 95th percentile during childhood; diastolic blood pressure greater than 95th percentile during childhood; dental caries in childhood.

Primary outcomes

(1) High blood pressure with or without proteinuria

Calcium supplementation was associated with a reduction in high blood pressure in five studies (665 women, RR 0.53, 95% CI 0.38 to 0.74; heterogeneity: Chi^2 = 2.55, df = 4 (P = 0.64); I^2 = 0%; test for subgroup differences: Chi^2 = 2.11, df = 2 (P = 0.35), I^2 = 5.2%; Analysis 6.1), including three studies of calcium supplementation alone (558 women, RR 0.57, 95% CI 0.39 to 0.82) and one of calcium plus linoleic acid (48 women, RR 0.20, 95% CI 0.05 to 0.82).

(2) Pre-eclampsia

Pre-eclampsia was reduced with low-dose calcium supplementation (nine studies, 2234 women, RR 0.38, 95% CI 0.28 to 0.52; I^2 = 0%; Analysis 6.2). The reduction was also consistent across the following subgroups: calcium alone (four studies, 980 women, RR 0.36, 95% CI 0.23 to 0.57); calcium plus linoleic acid (two studies, 134 women, RR 0.23, 95% CI 0.09 to 0.60); calcium plus vitamin D, (two studies, 1060 women: RR 0.49, 95% CI 0.31 to 0.78; 1060 women; I^2 = 17%) and in one trial of calcium plus antioxidants with low risk of bias (60 women, RR 0.24, 95% CI 0.06 to 1.01). Test for subgroup differences: Chi^2 = 2.55, df = 3 (P = 0.47), I^2 = 0%.

(3) Preterm birth

Overall, there was little or no effect on preterm birth for calcium with other supplements (six studies, 1290 women: average RR 0.83, 95% CI 0.34 to 2.03; I^2 = 64%; Analysis 6.3). Preterm birth was reduced in the experimental arm of one study of calcium supplementation alone (422 women, average RR 0.40, 95% CI 0.21 to 0.75; Analysis 6.3), but as it was not reported in the other three studies of calcium supplementation alone, the possibility of publication bias needs to be considered. For calcium plus vitamin D, the risk of preterm birth seemed to be increased with supplements (three studies, 760 women: RR 1.59, 95% CI 1.03 to 2.45; I^2 = 0%; Analysis 6.3).

(4) Admission to neonatal intensive care unit (ICU)

Admission to neonatal ICU was reported in only one trial of calcium supplementation alone, so the reduction in the calcium group may be due to publication bias (422 women: RR 0.44; 95% CI 0.20 to 0.99; Analysis 6.4).

(5) Stillbirth or death before discharge from hospital

There was no overall effect on the RR of a stillbirth or the baby dying before discharge from hospital (five trials, 1025 women: RR 0.48, 95% CI 0.14 to 1.67; heterogeneity: Chi^2 = 0.99, df = 4 (P = 0.91); I^2 = 0%; Analysis 6.5).

Secondary outcomes

(6) Placental abruption

Three studies reported this outcome and the event rates were too small for meaningful analysis (160 participants: RR 1.00, 95% CI 0.14 to 6.90; Analysis 6.6).

(7) Caesarean section

Caesarean section was reduced in two studies of calcium plus linoleic acid (134 women: average RR 0.55; 95% CI 0.35 to 0.87; heterogeneity: Tau^2 = 0.00; Chi^2 = 0.03, df = 1 (P = 0.86); I^2 = 0%), but not overall (four studies, 521 women, average RR 0.73; 95% CI 0.46 to 1.15; heterogeneity: Tau^2 = 0.13; Chi^2 = 7.48, df = 3 (P = 0.06); I^2 = 60%); Analysis 6.7.

(8) Severe pre-eclampsia

Four trials reported severe pre-eclampsia and there was no clear difference between the groups (246 participants: RR 0.40, 95% CI 0.14 to 1.15; I^2 = 0%; Analysis 6.8).

(9) Eclampsia

One trial of calcium supplementation alone reported eclampsia. There was no clear difference between the groups (168 women: RR 0.17, 95% CI 0.01 to 4.06; Analysis 6.9).

(10) Miscarriage (non-prespecified)

An unexpected finding in one small trial of calcium plus antioxidants, commencing at eight to 12 weeks of pregnancy, was a reduction in miscarriage in the calcium plus antioxidant group (60 women: RR 0.06, 95% CI 0.00 to 1.04; Analysis 6.10).

(11) Low birthweight (birthweight less than 2500 g)

The risk of having a baby with birthweight less than 2500 g was reduced with calcium supplementation plus linoleic acid (two studies, 134 women: RR 0.20, 95% CI 0.05 to 0.88; heterogeneity: Chi^2 = 0.00, df = 1 (P = 1.00); I^2 = 0%; Analysis 6.11).

(12) Neonate small-for-gestational age

There was no overall effect on the risk of the baby being born small-for-gestational age (four trials, 854 women: RR 0.81, 95% CI 0.54 to 1.21; heterogeneity: Chi^2 = 2.06, df = 3 (P = 0.56); I^2 = 0%; Analysis 6.12).

Sensitivity analysis

We had planned to exclude studies assessed to have inadequate allocation concealment or high risk of attrition bias, or both. However, five studies either did not conceal allocation (Marya 1987), had high levels of attrition (Asemi 2012; Asemi 2016; Bassaw 1998), or both (Rogers 1999) and we did not feel that removing these would result in a meaningful analysis. If further studies are added in future updates we will perform the sensitivity analysis.

High-dose (=/> 1 g) versus low-dose (< 1 g) calcium supplements (one trial with 262 women)

Only a single trial with 262 women is included in this dose comparison and results were reported for only four of our prespecified outcomes. The risk of **pre-eclampsia** appeared to be reduced in the high-dose group compared to the low-dose group (RR 0.42, 95% CI 0.18 to 0.96; Analysis 7.1); for other outcomes, although results were in the same direction, there was insufficient evidence to demonstrate any clear difference between groups (**preterm birth**: RR 0.31, 95% CI 0.09 to 1.08, Analysis 7.2; **eclampsia**: RR 0.32, 95% CI 0.07 to 1.53, Analysis 7.3; **stillbirth**: RR 0.48, 95% CI 0.13 to 1.83, Analysis 7.4).

DISCUSSION

Summary of main results

High-dose calcium supplementation

Our meta-analysis showed that calcium supplementation with at least 1 g of calcium approximately halved the risk of pre-eclampsia compared to placebo, with the confidence intervals estimating the true effect to be a risk reduction of between 35% and 69%. Women with an adequate dietary intake of calcium were the only subgroup where the confidence interval crossed the line of no effect. Nevertheless, the point estimate for this subgroup of women was a 38% risk reduction. The greatest risk reduction was for women at high risk of pre-eclampsia (variably defined; 78% reduction). The meta-analysis may be an over-estimate, as funnel plot asymmetry suggested a small-study effect or publication bias. In the largest study, the 8% reduction in pre-eclampsia had a confidence interval that crossed the line of no effect.

There was also a 35% reduction in the risk of gestational hypertension, with the greatest effect also amongst women with low calcium diets. These data should be interpreted with caution because of the possibility of small-study effects or publication bias.

The risk of having the composite outcome 'maternal death or severe morbidity' was reduced by 20% with calcium supplementation and there was a 24% reduction in the risk of preterm birth.

The risk of haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome was increased; however the absolute number of events was low (2.5/1000 versus 0.9/1000). There were no clear effects on other relevant outcomes at discharge from hospital. There were no clear differences between calcium supplementation and placebo for any other outcomes, although for several outcomes the confidence intervals approach statistical significance, e.g. for caesarean section a small (5%) reduction in risk associated with calcium supplementation is possible. For stillbirth and death before discharge from hospital, the point estimate is for a reduction of 10%, although no effect or a small increase in risk has not been excluded.

Low-dose calcium supplementation

The results with low-dose calcium supplementation alone are similar to those of the smaller studies with high-dose supplementation, showing a reduction in pre-eclampsia of about 60% which was consistent between studies with low and high risk of bias. High blood pressure with or without proteinuria was reduced by about 50%. Results for calcium plus other interventions were similar to those for calcium alone, but the possibility that the cointerventions contributed to the effect on pre-eclampsia needs to be considered. For antioxidants, this is unlikely as antioxidants have not been found to reduce the risk of pre-eclampsia (Rumbold 2008). For vitamin D there is as yet inadequate evidence regarding its effect on pre-eclampsia (De-Regil 2012); for linoleic acid there is also insufficient evidence. There were no other differences, other than a reduction in neonatal intensive care admission and low birthweight in the low-dose calcium supplementation groups. These outcomes were reported only by one or two studies, suggesting reporting bias.

High-dose versus low-dose calcium supplementation

One small study, which had limitations, found a reduction in pre-eclampsia with 2 g calcium daily versus 500 mg daily.

Overall completeness and applicability of evidence

We consider the evidence in favour of high-dose calcium supplementation with respect to reducing the risk of pre-eclampsia to be complete, particularly in women with low calcium diets and those at high risk. Although there were not individually significant reductions in the risk of death, severe pre-eclampsia, eclampsia, or admission to intensive care, the point estimates for these outcomes favoured calcium supplementation, and so moderate reductions in these outcomes remain possible. The compound outcome death or severe morbidity was significantly reduced by 20%.

Few side effects were recorded in the included trials. In two trials, the risk of HELLP syndrome was increased with calcium supplementation. A possible explanation for this apparently anomalous finding is that calcium supplementation in the second half of pregnancy may only reduce blood pressure rather than the underlying pre-eclamptic process. Lower blood pressures in the calcium group may have reduced the diagnosis of pre-eclampsia and, thus, medical interventions to curtail pregnancy, allowing more time for the pre-eclampsia to progress to HELLP syndrome (Hofmeyr 2007).

There remains little information about the long-term follow-up of children exposed to calcium in utero. One study evaluated childhood systolic hypertension and dental caries. The risk of both of these outcomes was significantly reduced, however, the latter effect was observed in a small subset of the children and the study was not originally designed to assess this outcome. These effects therefore need corroboration.

There is no information about any possible changes in the use of healthcare resources associated with calcium supplementation. It would seem plausible that a reduction in gestational hypertension and pre-eclampsia might lead to fewer antenatal visits, less antepartum hospital admissions and fewer inductions of labour. However, the included trials do not provide data on these outcomes.

This 2018 update has included data from trials using less than 1 g calcium daily (mostly 500 mg to 600 mg). Over half of these studies were at high risk of bias and combined calcium with other supplements. However, the evidence seems to indicate that lower doses of calcium may be effective in reducing hypertensive disorders of pregnancy. The results of the low-dose studies is therefore incomplete and need corroboration by larger high-quality studies.

Quality of the evidence

We consider the evidence for the effect of high-dose calcium supplementation on pre-eclampsia and preterm birth to be low, due to heterogeneity and small study effects. We deemed the evidence for HELLP syndrome to be of high quality (see Summary of findings for the main comparison). The quality of evidence for the large studies subgroup was also high.

In general, heterogeneity of findings seemed to be largely associated with study size, with the small studies having the most positive results (see Figure 4 to Figure 12). These small-study effects may indicate publication bias or other biases, or be caused by differences between small and large studies. As the small studies tended to recruit high-risk women, at least some of the heterogeneity may be explained by calcium having a greater effect for high-risk women. These data on heterogeneity related to sample size should be interpreted with caution however, as the sensitivity analysis was post-hoc, and the cut-off point for sample size (400) was arbitrary.

Potential biases in the review process

We sought to minimise potential biases in the review process by having clearly-defined criteria for inclusion of studies, and by excluding members of the review team from decisions regarding studies in which they were involved. Post hoc inclusions are clearly identified, and acknowledged as a potential source of bias.

Agreements and disagreements with other studies or reviews

This evidence of a modest risk reduction in gestational hypertension and 'maternal deaths and serious morbidity' contrasts with the large epidemiological differences previously identified between populations with adequate and low dietary calcium intake (Belizan 1980; Hamlin 1952; Hamlin 1962). Possible explanations include the following.

1. Dietary calcium may be a marker for other aetiological factors.
2. Starting supplementation in the middle trimester of pregnancy may be too late to be fully effective.

The finding of reduced childhood hypertension needs replication but, if corroborated, has far-reaching implications for public health. Although based on only a partial follow-up in one study (Belizan 1991), this finding is supported by a very limited follow-up in two other studies (CPEP 1997; Crowther 1999), as well as observational (McGarvey 1991), and animal (Bergel 2002) studies.

There are concerns regarding possible adverse effects of calcium supplementation, which may be dose-related. Long-term calcium use in later life has been associated with myocardial infarction, however the association may not be causal (Li 2012). In addition, in a 2010 publication of the Gambia study in which women received calcium supplementation of 1.5 g during pregnancy (Jarjou 2004), investigators reported reduced bone density in the women postpartum. They suggest that high-dose calcium during pregnancy might reverse metabolic adaptation to long-term low calcium diets, resulting in a rebound effect when withdrawn. This finding was based on a selected follow-up and was opposite to the prior hypothesis and therefore needs confirmation in a prospective study.

AUTHORS' CONCLUSIONS

Implications for practice

The possible reduction in hypertension, pre-eclampsia and preterm birth (low-quality evidence), and the reduction in the composite outcome 'maternal death or severe morbidity' (high-quality evidence) with high-dose calcium supplementation should be considered when making decisions about the use of calcium supplementation during pregnancy, particularly for those with low dietary intake or high risk of pre-eclampsia. Based on evidence included in the previous version of this review, which was limited to high-dose calcium supplementation, the World Health Organization recommends a calcium dose of 1.5 g to 2 g during pregnancy for women with low dietary calcium intake (WHO 2011). However, this recommendation may be associated with logistical difficulties in low-income countries: calcium is relatively expensive, and the tablets are bulky and heavy (about 1 kg for a 20-week supply of calcium carbonate and glycine, providing 1.5 g elemental calcium daily). Implementation may be subject to competing priorities in low-resource settings. The current updated review adds limited data on the effects of lower calcium dosage, which may guide pragmatic decisions in settings where high-dose supplementation is unachievable.

The increase in the risk of haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome was small in terms of absolute numbers. Therefore, we consider this limitation to be outweighed by the overall reduction in death or severe morbidity which is associated with calcium supplementation.

The one study which enrolled women with high risk of pre-eclampsia and adequate dietary calcium was too small to guide practice.

Evidence on the effects of calcium supplementation combined with low-dose aspirin (not included in this review) should also be considered.

Implications for research

Epidemiological studies have found a difference in dietary calcium intake between high- and low-income settings of about 500 mg. Doses of 1.5 g/day and higher are well above daily recommended dietary calcium intake. Some women find it difficult to swallow or chew three to four large tablets daily, which may affect adherence. Furthermore, doses in excess of 800 mg daily may inhibit iron absorption. Therefore, further research is necessary to determine the optimal dose of calcium supplements in pregnancy. It would also be relevant to assess whether supplementation via dietary modification, for women with low calcium intake, has the same benefits as the tablets administered in these trials.

Further research is needed to determine the effectiveness of calcium supplementation in women with high risk of pre-eclampsia and adequate dietary calcium.

Further research is also needed to provide reassurance that calcium supplementation during pregnancy does not have any adverse effects for the children exposed whilst in utero, and to verify whether it reduces childhood hypertension.

The increase in the risk of HELLP syndrome identified by this review requires further investigation. Any future trials should also collect information about the use of health service resources, as well as other clinical outcomes.

In most of the studies reviewed, supplementation was commenced around 20 weeks of pregnancy. In one small trial of low-dose calcium supplementation, commencing at eight to 12 weeks in high-risk women, there was an unanticipated trend to reduced miscarriage. This interesting observation needs to be explored further in prospective research.

We have hypothesised, based on the finding in this review of no effect of calcium supplementation on proteinuria, that the benefits of calcium supplementation in the second half of pregnancy may be the result of a direct lowering effect on blood pressure, and that supplementation may be needed from before pregnancy to affect the genesis of pre-eclampsia during placental development. This hypothesis is addressed in a separate review (Hofmeyr 2017).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Almirante 1998

Methods	"divided into two groups and followed up until delivery."
Participants	430 pregnant women who were nulliparas, adolescents and elderly. Dates of recruitment not stated. Setting not stated, Phillipines
Interventions	Group B: 212 women received 500 mg elemental calcium from 16-20 weeks till delivery. Group A: 210 women served as controls.
Outcomes	Pre-eclampsia, preterm birth, admission to NICU
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement

Almirante 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No record of loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	High risk	Abstract only, no details, no placebo

Asemi 2012

Methods	RCT described as single-blind controlled clinical trial Individual randomisation
Participants	Setting: maternity clinics in Kashan Iran. Dates of recruitment: April 2011 to February 2012. Inclusion criteria: pregnant nulliparous women at risk of pre-eclampsia, singleton pregnancy, 18-35 years in third trimester. High risk was defined as nulliparous, with environmental, socioeconomic factors or obesity (not clear). 54 women recruited. Exclusion criteria: women with severe pre-eclampsia, intrauterine fetal death, placental abruption, preterm birth or GDM.
Interventions	Experimental intervention: calcium-vitamin D supplements for 9 weeks (500 mg calcium carbonate plus 200 IU vitamin D per day). Total number randomised: n = 27 women (24 analysed). Control/comparison intervention: placebo. Total number randomised: n = 27 women (25 analysed).
Outcomes	Compliance monitored weekly. Dietary intake (from diaries). Maternal weight, BMI, blood biochemical outcomes (fasting plasma glucose, cholesterol, high and low density lipoprotein-cholesterol).
Notes	Funding: the study was supported from a grant (university or government). Grant from the Vice-chancellor for Research, Kashan University of Medical Sciences (KUMS). Study placebo provided by Share Darou Co, Tehran, Iran and supplements by Darou Pakhsh Co.

Asemi 2012 *(Continued)*

	CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	This was a placebo controlled study but it was not clear how women were assigned to groups. Although the supplements and placebo packs were described as identical it was not clear whether or not staff were aware of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as a single-blind trial. It was not clear what this meant. Women were provided with active or placebo drugs in identical packs. Only participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not clear if outcome assessment was blind but as most outcomes were biochemical lack of blinding may not have impacted on outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	54 women were recruited, 49 included in the analyses (25 in placebo group, 24 in calcium/vitamin D group). Women with severe pre-eclampsia, preterm birth and GDM were excluded — it was not clear if these exclusions were after randomisation — these outcomes may have related to the intervention.
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol. It was not clear if all outcome data collected was reported.
Other bias	Unclear risk	Women in the placebo group had slightly lower weights pre-pregnancy (and throughout pregnancy).

Asemi 2016

Methods	Double-blind parallel-arm RCT, individual randomisation, placebo controlled
Participants	Setting: clinics in Kashan, Iran. Dates of recruitment: March-September 2012. Inclusion criteria: 46 women, 18-40 with singleton pregnancy. Exclusion criteria: women with pre-eclampsia, placental abruption and GDM (it appeared that women were excluded after randomisation).
Interventions	Experimental intervention: calcium-vitamin D for 9 weeks from 25 weeks (500 mg calcium, 200 IU vitamin D per day). Total number randomised: n = 23. Control/comparison intervention: placebo pills of similar appearance. Total number randomised: n = 23. Women in both groups took iron and folic acid supplements.

Asemi 2016 *(Continued)*

Outcomes	Fasting plasma glucose, insulin metabolism, biomarkers of oxidative stress, vitamin D levels, BP, birth size, gestational age, mode of birth.
Notes	Author contacted re information about women excluded after randomisation. Funding: reported to be funded by a grant from the vice-chancellor for research, Kashan university of medical sciences. Reported that supplements and placebo were provided by Shahre Daru Co, Tehran. CoI: reported no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It was reported that randomisation was by random numbers "taken from a computer".
Allocation concealment (selection bias)	Unclear risk	Placebo controlled but method at point of randomisation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear if staff blind. Placebo controlled but it was not clear if staff were aware.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if outcome assessors blind, some outcomes may not be affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	4 women were excluded post-randomisation for reasons that may have related to the intervention (participants that developed complications during the trial were excluded – we have added these back in and collected these data for our analysis).
Selective reporting (reporting bias)	Unclear risk	We had no protocol. Women were excluded post-randomisation and no ITT.
Other bias	Unclear risk	Author contacted re post-randomisation exclusions.

Bassaw 1998

Methods	Randomised clinical trial. Participants were alternately allocated to either the supplemented or to the control groups in order to match for age, parity, ethnic group and BMI. Data from the 'control' group were not used in this analysis. Randomisation was conducted by the pharmacist using a table of random numbers, and supplements were distributed to the participants in sealed envelopes. Clinicians were unaware whether the participants were in the supplemented or control groups, and which supplementation was administered.
Participants	Women attending a hospital in Trinidad between 1992 and 1995. Pregnant women recruited into the study before 20 weeks' gestation primigravidae, or multigravidae with obstetric history of pre-eclampsia. Participants were normotensive and urinalysis was negative for albuminuria. None had any underlying medical disorders such as chronic hypertension, renal disease, diabetes mellitus and collagen vascular disorders.

Bassaw 1998 *(Continued)*

Interventions	2 calcium tablets (1200 mg elemental calcium), a combination of 1 calcium tablet and 1 baby Cafenol (80 mg aspirin) or 1 baby Cafenol daily. All participants, including the controls, received the routine haematinics which were ferrous sulphate (200 mg) and folic acid (5 mg) daily. There were 114 primigravidae amongst the controls. Of the supplemented groups, 45 primigravidae received aspirin, 36 had calcium and aspirin, and calcium tablets were administered to 42 primigravidae. All of these women were less than 24 years of age. For this review we have used only data for calcium (600 mg) and Cafenol (80 mg aspirin) vs Cafenol daily (80 mg aspirin).
Outcomes	DBP (measured by the same observer with the participants in a sitting position, recorded at the onset of muffing -phase 4 Korotkoff sound), PIH (BP ≥ 140/90 mmHg), pre-eclampsia (hypertension plus proteinuria).
Notes	8 participants were unavailable for analysis. Source of funding: not stated. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The supplement vs control group were allocated by alternation, but it was clear that various supplemented groups were randomised by the pharmacist using random number tables. In this review we use only data for calcium plus aspirin vs aspirin, which were randomised.
Allocation concealment (selection bias)	Low risk	Supplements were distributed in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Clinicians were unaware whether the participants were in the supplemented or control groups, and which supplementation was administered. Participants were not blinded as placebos were not used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported that clinicians recording outcomes were unaware of treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	8 participants were unavailable for analysis.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	None noted

Belizan 1991

Methods	Multicentre trial. Numbered, sealed opaque envelopes, containing randomisation codes. Of 593 (calcium) vs 601 (placebo) enrolled, 14 vs 13 were lost before starting treatment and excluded from analysis;

Belizan 1991 *(Continued)*

	577 vs 588 had at least partial follow-up. Follow-up was incomplete for 52 vs 46, but delivery data were available in 17 vs 12 of these, giving delivery data for 544 vs 554.
Participants	Nulliparous women, < 20 weeks' pregnant; BP < 140/90 mmHg (mean of 5 measurements); no present or past disease; not taking medication; normal oral glucose tolerance tests. Recruitment between 1987 and 1989.
Interventions	2 g calcium as 500 mg calcium carbonate tablets, vs identical looking placebo tablets. Compliance was 84% (calcium) and 86% (placebo).
Outcomes	Gestational hypertension (DBP 90 or more; SBP 140 or more mmHg, on 2 occasions 6 hours apart); pre-eclampsia (gestational hypertension + proteinuria > 0.3 g/L on 2 random urine samples 6 hours apart); BP measured with random-zero sphygmomanometers, Korotkoff sound 5. Perinatal death. Follow-up: BP > 95th percentile for sex, age and height for children 5-9 years.
Notes	3 hospitals in Rosario, Argentina. Data for preterm birth given as percentages, not clear what the denominators were. Assumed to be the numbers with complete follow-up (527 vs 542) as these were the numbers which were divisible by the percentages to give whole numbers. Unpublished placental abruption data obtained from authors. Babies born in the private hospitals followed up at 7 years. Of 614 randomised (calcium 309/placebo 305), 301/299 completed the first study, 2/6 infant deaths and 1/0 maternal deaths had occurred, leaving 298/293 eligible for follow-up. 289/285 were contacted, 10/5 refused to participate, 22/19 lived outside the country, and 257/261 were assessed (88% of those eligible). Funded by a research grant from The International Development Research Centre, Canada. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence - Epistats Statistical Package
Allocation concealment (selection bias)	Low risk	Complete set of numbered sealed opaque envelopes was sent to each of 3 hospitals.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation code was held centrally such that the woman and her health-care providers were blind to her trial group. Tablets were identical in appearance, weight, colour, taste.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation code was held centrally such that the woman and her health-care providers were blind to her trial group. Tablets were identical in appearance, weight, colour, taste.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All or partial data available for 579/593 (Ca) and 588/601 (Pl) respectively. Delivery data were available for 544 and 554 respectively.
Selective reporting (reporting bias)	Low risk	All primary outcomes addressed
Other bias	Low risk	Balanced group sizes, baseline characteristics including dietary calcium similar in both groups

Cong 1995

Methods	"Healthy antepartum cases were randomized and divided into 3 groups."
Participants	Healthy primipara. Setting and dates of recruitment not stated (China)
Interventions	A: 120 mg calcium daily; B: 240 mg calcium daily; C: no calcium (D: 1 g calcium; E: 2 g calcium; E: no calcium: not included as trials with high risk of bias not included in high calcium dose review).
Outcomes	Biochemical studies; hypertension, pre-eclampsia, birthweight, gestational age, method of delivery.
Notes	First period (low dose) April 1987 to June 1988 (groups A, B, C); second period (high dose) April 1989 to June 1990 (groups C, D, F). Similar results for groups A and B, which were combined in this meta-analysis Source of funding: not stated. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Limited information
Other bias	High risk	Very limited description of methods

CPEP 1997

Methods	Numbered treatment packs in computer-generated simple randomisation sequence. Loss to follow-up: calcium 132/2295 vs placebo 121/2294.
Participants	Setting: medical centres in the USA. Dates of recruitment not clear.

CPEP 1997 *(Continued)*

	Pregnant nulliparas (45% black, 35% non-Hispanic white, 17% Hispanic white). Passed compliance test (took 75% of placebo over 6-14 days); BP 134/84 mmHg or less; urine protein dipstick negative or trace; 13-21 weeks' pregnant. Exclusion criteria: taking medications; obstetric or pre-existing diseases or personal characteristics which could influence study end points, absorption or metabolism of calcium; any risk associated with calcium supplementation, or compliance; elevated serum creatinine (1.0 mg per dL or more) or calcium (10.6 mg per dL or more); renal disease; haematuria; history or family history of urolithiasis; frequent use of calcium supplements or antacids. Of 11,959 women screened, 5703 were excluded initially and a further 1667 after the compliance test. The remaining 4589 women were enrolled.
Interventions	2 g/day elemental calcium as calcium carbonate, or placebo. Taken until delivery, development of pre-eclampsia or suspicion of urolithiasis. All women took 50 mg calcium per day as normal supplementation and were asked to drink 6 glasses of water per day. Compliance was 64% in the calcium group and 67% in the placebo group. 20% of women took > 90% of the allocated treatment.
Outcomes	Gestational hypertension (DBP sitting, fifth Korotkoff sound unless zero, 90 mmHg or more on 2 occasions, 4 hours to 1 week apart); severe gestational hypertension (DBP 110 mmHg twice or treated, or complications); proteinuria (300 mg/24 hours or more, 1+ on 2 occasions 4 hours to 1 week apart, 2+ or more, or protein/creatinine ratio 0.35 or more); pre-eclampsia (gestational hypertension + proteinuria within 7 days of each other); severe pre-eclampsia (50/2163 vs 59/2173); renal insufficiency (21/2163 vs 23/2173); urolithiasis (1/2163 vs 3/2173); prematurity (< 37 weeks); baby small-for-gestational age (124/2163 vs 105/2173); perinatal death. A limited follow-up of mothers and infants found to have reduced SBP at 2 years of age in the calcium supplementation group (mean 95.4 mmHg, SD 7.6, n = 35 vs 100.2, 7.9, n = 18). The data have not been included in this review because of the low and unequal follow-up rate (35 and 18 from 497 invited to participate) limit the reliability of the results.
Notes	Multicentre trial, 5 US university centres. Maternal outcomes reported as percentages of the whole number enrolled. In this review, denominators of 2163 (calcium) and 2173 (placebo) have been used. Neonatal outcomes in the report are based on live births (2134 and 2139). Addition of abortions and fetal deaths brings these numbers to 2156 and 2166. It is not clear why a discrepancy in numbers remains. Sources of funding: supported by The National Institute of Child Health and Human Development and the National Heart, Lung and Blood Institute. Study medications were industry provided. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Packages of study tablets were prepared and numbered by pharmaceutical manufacturer according to a computer-generated simple randomisation sequence.
Allocation concealment (selection bias)	Low risk	On enrolment, each woman was assigned the next numbered package of medication at 1 of 5 centres. The blister-packed tablets were identical in appearance.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. The code was held centrally.

CPEP 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. The code was held centrally.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 10%
Selective reporting (reporting bias)	Unclear risk	Authors used total number of women enrolled to each group as denominator instead of total number minus those lost to follow-up. Also small discrepancy in overall numbers but unlikely to affect results substantially.
Other bias	Low risk	Baseline characteristics similar

Crowther 1999

Methods	Central telephone randomisation, stratified by centre using variable blocks. Double-blind.
Participants	Inclusion criteria: nulliparous women; singleton pregnancy; < 24 weeks' gestation; BP < 140/90 mmHg; expected to give birth at a collaborating centre. Exclusion criteria: antihypertensive therapy; medical contraindication to calcium supplementation.
Interventions	Calcium carbonate 1.8 g daily or lactose placebo tablets, from 20-24 weeks until birth.
Outcomes	Primary: PIH (DBP 90 mmHg or more on 2 consecutive occasions 4 hours apart, or 110 mmHg once; pre-eclampsia (as above plus proteinuria 0.3 g or more per 24 hours or 2+ protein or more on 2 random clean-catch urine samples); preterm birth (< 37 weeks). Secondary: severe PIH (DBP 110 or more on 2 occasions 4 hours apart, or 120 or more once); severe pre-eclampsia (as above plus proteinuria); very preterm birth (< 32 weeks; extremely preterm birth (< 28 weeks); maternal fetal and infant events after trial entry.
Notes	5 hospitals in Australia. August 1992 to December 1996. Estimated sample size 948. Trial stopped prematurely for financial reasons. 31% in the calcium group and 24% in the placebo group stopped taking the tablets during the trial. Analysis was by ITT Sources of funding: a grant from the Queen Victoria Hospital Foundation and The Women's and Children's Hospital Foundation, Australia. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation centrally co-ordinated using variable blocks
Allocation concealment (selection bias)	Low risk	Identical sealed treatment packs prepared by drug company
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Tablets identical in size, colour and consistency. Code held centrally and only broken after trial closure and exploratory data analyses.

Crowther 1999 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Tablets identical in size, colour and consistency. Code held centrally and only broken after trial closure and exploratory data analyses.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 10%
Selective reporting (reporting bias)	Low risk	ITT analysis. 227 in calcium group and 229 in placebo group. Baseline characteristics similar.
Other bias	Unclear risk	Only achieved 48% of recruitment target (456 instead of 948) due to lack of funds.

Herrera 1998

Methods	Allocation sequence was generated using random number tables, and prepared by an administrative staff member.
Participants	Recruitment May 1995 to May 1996, 3 hospital outpatient clinics in Cali, Colombia. 676 healthy primigravid women screened. Primigravidas with risk factors for pre-eclampsia (high biopsychosocial risk, positive roll-over test and high mean BP (> 85 mmHg) selected).
Interventions	450 mg linoleic acid plus 600 mg calcium (n = 44) vs identical looking placebos (n = 45) in the third trimester.
Outcomes	Biochemical studies; maternal and neonatal clinical outcomes.
Notes	1 study group excluded for taking ASA; 2 from control group lost to follow-up Source of funding: the study was supported by a grant from the National Institute of Science and Technology of Colombia. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“ allocated randomly.”
Allocation concealment (selection bias)	Low risk	“ allocated randomly.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Double blind, placebo controlled trial.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“Double blind, placebo controlled trial.”

Herrera 1998 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 from study group excluded for taking ASA; 2 from control group lost to follow-up.
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	Low risk	"Double blind, placebo controlled trial."

Herrera 2006

Methods	"The participants were allocated in two random groups."
Participants	March 2001 to March 2003; 4 outpatient clinics in Bangladesh and Colombia. 220 primigravid women screened for abnormal Doppler ultrasound in uterine or arcuate arteries (diastolic notch) from week 18 to 22 of gestation. Primigravidas < 19 years or > 35 years, 18 to 22 weeks with risk factors for pre-eclampsia including reliable family history of PE were included. Those with DBP of 85 mm Hg or more at the first antenatal visit, cardiovascular or renal disease, or hypertensive or taking any medication at the time were excluded. Mean daily calcium intake was also similar at study entry (601.5 mg [range, 310—1101 mg] vs 576.0 mg [314—936 mg]; P = 0.94).
Interventions	450 mg conjugated linoleic acid plus 600 mg calcium (n = 25) vs placebo (n = 25) from 18 to 22 weeks.
Outcomes	Biochemical studies.
Notes	220 women screened; eco-Doppler ultrasound positive in 53 women; 3 eligible women refused to participate 1 woman from the control group was lost during the follow-up (change of residence) and 1 woman from the supplemented group withdrew. Source of funding: Columbia Institute for Science and Technology and Partners in Population and Development Institute, Dhaka, Bangladesh. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random cards were prepared and sealed by an independent administrative staff member using a random number table prepared with the True Epistat statistical package version 5.0."
Allocation concealment (selection bias)	Low risk	"allocated in two random groups….sequentially numbered, sealed, opaque envelope containing a card that indicated the study allocation."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"allocated in two random groups….sequentially numbered, sealed, opaque envelope containing a card that indicated the study allocation." - it appears the study was not double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"allocated in two random groups….sequentially numbered, sealed, opaque envelope containing a card that indicated the study allocation." - it appears the study was not double-blinded.

Herrera 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 loss to follow-up in each group
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Low risk	Low to moderate (appears not double-blind)

Jarjou 2004

Methods	Randomised double-blind placebo-controlled trial conducted in The Gambia between 1995 and 2000.
Participants	662 pregnant women were randomised; 452 of 546 live born children were followed up.
Interventions	1500 mg calcium (Ca) orally per day or placebo from 20 weeks' gestation until delivery.
Outcomes	1. Maternal BP at 36-38 weeks' gestation 2. Breast-milk calcium concentration during lactation 3. Postpartum bone mineral content of mother and baby 4. Cardiovascular risk in offspring 5. BP in offspring (Hawkesworth 2011). Follow-up of 350 children (64%). There were no differences in mean BP measurements 6. Maternal plasma 25 hydroxyvitamin D, birthweight and infant growth and bone mineral accretion (Prentice 2009)
Notes	Source of funding: UK Medical Research Council. (Supplements and placebos were provided by a pharmaceutical company.) CoI: none of the authors reported a personal or financial conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random permuted blocks of 4
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	> 20% missing data

Jarjou 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Maternal hypertension outcomes have not yet been reported
Other bias	High risk	Of 155 women randomised, 125 who had normal pregnancy were selected for the sub-studies. It's not clear whether bias could have been introduced by this selection.

Khan 2013

Methods	Described as prospective randomised clinical trial
Participants	Setting: women attending the antenatal clinic of a tertiary care hospital in West Bengal, India (described as serving a population with low socio-economic status). Dates of recruitment: May 2010–April 2011. Inclusion criteria: 272 women. Healthy nulliparous women (18-30 years) with singleton pregnancy, with BP < 140/90 mmHg and no proteinuria at first antenatal visit before 20 weeks.
Interventions	Experimental intervention: 127 women. High-dose calcium supplements (2 g oral elemental calcium, 4 tablets daily) from 20 weeks' gestation. Comparison intervention: 145 women. Low-dose calcium (500 mg plus placebo, 1 active and 3 placebo tablets of similar appearance daily).
Outcomes	(Prespecified outcomes were not clear; it was stated what was recorded at subsequent antenatal visits but it was not clear if these were study outcomes). Reported: eclampsia and pre-eclampsia, preterm birth, gestational age at birth, birthweight, IUGR, stillbirth, mean systolic and mean BP (not clear when the reported values were measured).
Notes	Funding: not stated. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reported using a computer-generated randomisation table
Allocation concealment (selection bias)	Unclear risk	This was reported to be a placebo controlled trial but it was not clear staff were aware of allocation at the point of randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo was supplied so women may have been blind to which arm they were in. It was not clear whether staff were aware of the treatment group.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not clear if it was recorded in notes whether women were in the intervention or placebo groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/272 were lost to follow up.

Khan 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	We had no trial protocol and it was not clear what the study outcomes were (much data that was collected were not reported). Several outcomes were not well defined (e.g. not clear when mean BP values were recorded).
Other bias	Unclear risk	No baseline characteristics reported

Kumar 2009

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Women were recruited between January 2005 and December 2007 at a hospital in New Delhi, India. Healthy normotensive primigravid women with uncomplicated single pregnancy; pregnancy 12 to 25 weeks' gestation, known date of the last menstrual period, and intention to deliver at Lok Nayak Hospital, New Delhi. Study population had a low dietary calcium. Exclusions: multiple pregnancy, polyhydramnios, fetal malformations, diabetes, chronic hypertension, renal disease, cardiovascular disease, urolithiasis, or BP of 140/90 mmHg or higher at first visit or at enrolment.
Interventions	4 tablets (2 g calcium or placebo) were taken daily.
Outcomes	Pre-eclampsia (SBP > 140 mmHg and DBP > 90 mmHg on 2 occasions 4 hours apart after 20 weeks' pregnancy in women normotensive previously, together with proteinuria > 300 mg/24 h or 1+ on a clean-catch dipstick in the absence of urinary infection); eclampsia; preterm delivery; caesarean section. Baseline characteristics comparable.
Notes	Imbalanced groups: 290 allocated to calcium, 262 to placebo group. 17 and 11 lost to follow-up so 273 and 251 analysed respectively. See below. Source of funding: University Grant Commission, New Delhi, India. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Simple randomisation sequence developed manually
Allocation concealment (selection bias)	Low risk	Coded numbers assigned to treatment packets and distributed to participants using the random number sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Calcium and placebo tablets were identical. Randomisation code broken after completion of the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Calcium and placebo tablets were identical. Randomisation code broken after completion of the trial.
Incomplete outcome data (attrition bias)	Low risk	Attrition < 10%

Kumar 2009 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	High risk	Imbalance in size of groups. The authors were contacted regarding the imbalance and they explained that a random sequence was generated for 600 participants (unblocked) but recruiting was stopped at 552 participants and so 48 numbers remained unallocated.

L-Jaramillo 1989

Methods	Assigned independently in sequence using a table of random numbers. All 106 women enrolled completed the study (calcium 55, placebo 51), 14 women who delivered at 36-38 weeks excluded (calcium 6, placebo 8), none developed gestational hypertension. These women are included in this review.
Participants	Women recruited at a hospital antenatal clinic in Quito, Ecuador. Dates of recruitment 1984-1986. Inclusion criteria: nulliparity; age 25 years or less; certain menstrual dates; clinic attendance before 24 weeks' gestation; residence in Quito; normotensive; no medical disorders; not taking medication or vitamin/mineral preparations.
Interventions	Calcium supplementation with 4 calcium gluconate tablets daily, each containing 500 mg elemental calcium, from after 23 weeks' gestation till delivery, vs identical placebo tablets.
Outcomes	Gestational hypertension (BP 140/90 mmHg or more, or rise of 30 mmHg systolic or 15 mmHg diastolic, on 2 occasions 6 hours apart); weekly weight gain, mean (SEM) (calcium 412 (26) vs placebo 452 (28) g); birthweight (3097 (40) vs 2832 (50) g); length of gestation (39.3 (0.08) vs 38.7 (0.07) weeks).
Notes	Quito, Ecuador (altitude 2800 m). 1984 to 1986. An earlier report of apparently the same study gave an incidence of gestational hypertension of calcium 3/46 vs placebo 13/46 (Lopez-Jaramillo 1987). Source of funding: the study was supported by the Consejo Nacional de Ciencia y Technologia and Consejo Nacional de Universidades y Escuclas Polieenicas, Ecuador. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assigned using a random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind. Identical containers and tablets prepared by the Faculty of Chemistry and Pharmacy, Central University of Ecuador.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind. Identical containers and tablets prepared by the Faculty of Chemistry and Pharmacy, Central University of Ecuador.

L-Jaramillo 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	14 women excluded from the report because they delivered before 38 weeks leaving 43/49 women in the calcium and placebo groups respectively. Data from the 14 excluded women are included in this review.
Selective reporting (reporting bias)	Unclear risk	Not clear
Other bias	Unclear risk	Not clear

L-Jaramillo 1990

Methods	Randomised, double-blind trial. Stated "Each patient was assigned independently in sequence", and "All women completed the study".
Participants	Women attending a hospital in Quito, Ecuador. Dates of recruitment not stated. Healthy nulliparous women with positive roll-over test at 28-30 weeks' gestational age - judged at high risk for gestational hypertension.
Interventions	2000 mg elemental calcium daily, from 28-32 weeks to delivery, vs placebo starch tablets.
Outcomes	Gestational hypertension (BP > 140/90 mmHg on 2 occasions 6 hours apart); proteinuria (300 mg/L); duration of pregnancy (calcium mean 39.2 (SD 1.2) vs placebo 37.4 (2.3) weeks); birthweight (2936 (396) vs 2685 (427) g).
Notes	Quito, Ecuador (altitude 2800 m). 22 in calcium group, 34 in placebo group. Source of funding: not stated. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors state that this was a RCT but no details of sequence generation are provided.
Allocation concealment (selection bias)	Unclear risk	No details given about how concealment was achieved or whether tablets looked identical
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated double-blind but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated double-blind but no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear
Selective reporting (reporting bias)	Unclear risk	Not clear

L-Jaramillo 1990 *(Continued)*

Other bias	Unclear risk	Large discrepancy in size of groups not accounted for

L-Jaramillo 1997

Methods	Prospective, randomised, double-blind, placebo-controlled trial.
Participants	Hospital setting in Quito Ecuador, women recruited 1990-1995. Inclusion criteria: age < 17.5 years; nulliparous; first prenatal visit before 20 weeks' gestation; certain menstrual dates; residency in Quito for at least 1 year; BP =/< 120/80 mmHg; no underlying medical disorders; no drug, mineral or vitamin therapy. Average daily calcium intake in this population is 51% of the recommended dietary allowance.
Interventions	Elemental calcium 2 g daily as calcium carbonate from 20 weeks (n = 134), vs placebo tablets (n = 140).
Outcomes	Pre-eclampsia (BP > 140/90 mmHg on 2 occasions > 6 hours apart, and proteinuria > 300 mg/L (> 1+ on dipstick on 2 occasions 4-24 hours apart)). BP recorded as mean of 2 measurements, 2 minutes apart, in the right arm, in the sitting position (1st and 5th Korotkoff sounds). Maternal serum ionised calcium at 38 weeks was calcium group mean 1.23, SD 0.02 mM vs placebo 1.16, 0.02; umbilical cord serum ionised calcium levels were calcium 1.44, 0.04 vs placebo 1,37, 0.03; gestational length was calcium 39.6, 0.4 vs placebo 38.7, 0.3.
Notes	Quito, Ecuador (altitude 2800 m). 1990 to 1995. Source of funding: supported by the Safe Motherhood Program, World Health Organization. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used to assign each participant independently in sequence to calcium or placebo regimen
Allocation concealment (selection bias)	Low risk	Adequate. Tablets similar in weight, colour, size. Containers and tablets prepared by the Department of Chemistry and Pharmacy, Central University of Ecuador
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	274 recruited, 260 analysed
Selective reporting (reporting bias)	Unclear risk	Only participants with no missing values were included in the analyses (125 in calcium group and 135 in placebo group).

L-Jaramillo 1997 *(Continued)*

Other bias	Unclear risk	14 withdrawals after randomisation: 12 by change to another hospital or private medical doctor, 2 by non-compliance. 9/134 (6.7%) were from the calcium group and 5/140 (3.6%) from the placebo group.

Li 2000

Methods	"Patients were divided into 3 groups."
Participants	Women recruited at the outpatient clinic and labour ward of the First Afifliated Hospital of Xi'an Medical University between Aug 1996 to Dec 1998. High-risk women with a predisposition to PIH. Participants were required to be at 20-24 weeks' gestation when entering the study, with a BMI index of < 24, and an arterial pressure of < 11.3 kPa. Study states only that participants were "selected from our hospital outpatient clinic and labour ward".
Interventions	The first group (n = 29) received a daily dose of 600 mg of Calictrate-D, the second group (n = 29) received 1200 mg if Calcitrate-D daily, and the third group (n = 30), the control group, received nothing. From 20-24 weeks till birth
Outcomes	Hypertension; biochemical studies
Notes	The outpatient clinic and labour ward of the First Afifliated Hospital of Xi'an Medical University. Aug 1996 to Dec 1998. No information on consent or ethical approval Source of funding: not clear (original article not in English). CoI: not clear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	High risk	Methods not reported

Marya 1987

Methods	"Randomly selected." Information from authors indicated that it was actually a consecutive series.
Participants	Women attending the antenatal hospital of a hospital in India. Dates of recruitment not stated. 400 pregnant women 20 to 35 years old attending antenatal clinic. Dietary intake about 500 mg calcium and 40 IU vitamin D daily.
Interventions	200 women daily supplement calcium 375 mg plus vitamin D 1200 IU from 20 to 24 weeks of pregnancy onwards, vs 200 women no supplement.
Outcomes	"Toxaemia", biochemical studies, mean BP
Notes	Medical College Hospital, Rohtak, India Souce of funding: not stated. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not specified. Information from authors indicated that it was actually a consecutive series.
Allocation concealment (selection bias)	High risk	Not specified. Information from authors indicated that it was actually a consecutive series.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No record of losses to follow-up
Selective reporting (reporting bias)	Unclear risk	No report of registered protocol
Other bias	High risk	Very limited reporting of methods

Niromanesh 2001

Methods	Double-blind, placebo-controlled clinical trial.
Participants	Women attending a hospital in Tehran, Iran. Dates of recruitment not stated Women at high risk for pre-eclampsia: positive 'roll-over' test and at least 1 risk factor for pre-eclampsia; 28-32 weeks' pregnant; BP < 140/90 mmHg. Exclusion criteria: chronic medical conditions.

Niromanesh 2001 *(Continued)*

	Not defined as low or adequate calcium intake (from table 1 dairy intake appears to be about 200 mL + 400 g per day)
Interventions	Elemental calcium 2 g daily (500 mg 6-hourly) or placebo, coded by the pharmacy
Outcomes	Pre-eclampsia: an increase (30 mmHg) of SBP above 14 mmHg and an increase (15 mmHg) of DBP above 90 mmHg, twice 4-6 hours apart, with proteinuria 1+; duration of pregnancy (39.5 SD 0.8 vs 37.7 SD 2.5 weeks); birthweight (3316 SD 308 vs 2764 SD 761 g); weekly maternal weight increase (no difference).
Notes	No loss to follow-up Source of funding: not stated; supplements and placebo tablets were provided by a pharmaceutical company. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Women were "randomly assigned".
Allocation concealment (selection bias)	Low risk	Adequate. Manufacturer coded the tablets which had same packaging and physical characteristics. A pharmacy dispensed the tablets.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data (sample size = 30)
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	No incomplete data or loss to follow-up

Purwar 1996

Methods	Prospective, randomised, double-blind, placebo-controlled trial. Allocated by means of a computer-generated randomisation list. After randomisation, 11/201 (5.5%) women were lost to follow-up (calcium 6, placebo 5).
Participants	Women attending a hospital clinic in Nagpur, India. Recruitment between 1993 and 1994. Calcium intake mean 336 mg (calcium) and 352 mg (placebo group) per day. Inclusion criteria: nulliparity; normal single viable pregnancy; known dates; antenatal clinic before 20 weeks; intending to deliver in the same institute; normal glucose tolerance test; no hypertension; no underlying medical disorders.

Purwar 1996 *(Continued)*

	Exclusion criteria: renal disease; collagen vascular disease; chronic hypertension; endocrinological disease; taking medication.
Interventions	Oral calcium containing 2 g elemental calcium daily (n = 103), compared with identical placebo tablets (n = 98), taken from 20 weeks
Outcomes	Gestational hypertension (SBP > 140 mmHg and DBP > 90 mmHg, twice 6 hours apart) and pre-eclampsia (hypertension + proteinuria =/> 0.3 g/24 hours)
Notes	Nagpur, India Source of funding: not stated. Supplements and placebos were provided by a pharmaceutical company. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Containers and tablets prepared by a pharmaceutical firm in Nagpur. Tablets were the same size, weight and colour.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Containers and tablets prepared by a pharmaceutical firm in Nagpur. Tablets were the same size, weight and colour.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 10%
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Apart from 11 women lost to follow-up, there are no missing data. Otherwise baseline characteristics and compliance were similar; balanced loss to follow-up.

Rogers 1999

Methods	Randomised to control vs aspirin vs calcium in ratio 1; 2; 2, using 5 unsealed envelopes, selected by participants. Imbalance suggested that ‘something went wrong’, perhaps a tendency for participants to select from a certain part of the pile of envelopes.
Participants	Women attending a clinic in Hong Kong. Recruitment: July 1992 to Dec 1994.

Rogers 1999 *(Continued)*

	500 primiparous Chinese women in 2nd trimester with sitting MAP 80 to 106 mmHg screened at 22-24 weeks with rested left lateral automated BP (cut-off MAP 60 mmHg). 369 selected: calcium 154, aspirin 132, control 83. 32 delivered elsewhere and were excluded, leaving 337.
Interventions	Aspirin 80 mg daily from 22 weeks vs calcium 600 mg daily from 22 to 32 weeks, then 1200 mg daily vs control
Outcomes	Hypertension, pre-eclampsia, mean BP
Notes	Source of funding: not stated. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	5 open envelopes
Allocation concealment (selection bias)	High risk	Unsealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	10% loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	High risk	See above

Rumiris 2006

Methods	Double-blind, placebo-controlled trial. Participants randomised according to a computer-generated random number sequence by an independent third party who had no conflict of interest in the study.
Participants	Women attending a university hospital in Indonesia between March 2003 and June 2004 60 pregnant women with low antioxidant status at 8 to 12 weeks of gestation Exclusion criteria: 1) history or current use of anti-hypertensive medication or diuretics; 2) use of vitamin C > 150 mg and/or vitamin E > 75 IU per day; 3) known placental abnormalities;

Rumiris 2006 *(Continued)*

	4) current pregnancy as a result of in vitro fertilisation; 5) regular use of platelet active drugs or non-steroidal anti-inflammatory drugs (NSAIDs); 6) known fetal abnormalities; 7) documented uterine bleeding within a week of screening; 8) uterine malformations; 9) history of medical complications.
Interventions	Supplementation with calcium (800 mg), N-acetylcysteine (200 mg), Cu (2 mg), Zn (15 mg), Mn (0.5 mg), and selenium (100 mcg) and vitamins A (1000 IU), B6 (2.2 mg), B12 (2.2 mcg), C (200 mg), and E (400 IU), from 8 to 12 weeks of gestation throughout pregnancy Both groups received Fe (30 mg) and folic acid (400 mcg). Placebo supplement's size and appearance were matched with those of antioxidants.
Outcomes	Maternal: pre-eclampsia, hypertension, proteinuria and abortion. Perinatal: IUGR, intrauterine fetal death, preterm delivery (before 37 weeks).
Notes	Source of funding: not stated. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised according to a computer-generated random number sequence by an independent third party who had no conflict of interest in the study.
Allocation concealment (selection bias)	Low risk	Participants were randomised according to a computer-generated random number sequence by an independent third party who had no conflict of interest in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to comment
Other bias	Low risk	None noted

S-Ramos 1994

Methods	Double-blind placebo-controlled trial. 4/33 allocated calcium lost to follow-up.
Participants	Women attending a hospital in Jacksonville, Florida, USA between 1989 and 1993. University hospital serving low-income population Normotensive nulliparas; positive roll-over test (281/1065) and positive angiotensin II infusion test at 20-24 weeks' gestation (67/281). 67 were allocated to calcium (33) or placebo (34). Exclusion criteria: factors increasing the risk of gestational hypertension, including renal disease, collagen vascular disease, diabetes mellitus, chronic hypertension, multifetal pregnancy.
Interventions	Calcium supplementation with 2 g per day elemental calcium as 500 mg calcium carbonate tablets, vs identical placebo tablets. Compliance checked with electronic pillboxes. Compliance was 79% vs 81%.
Outcomes	Gestational hypertension (BP at least 140/90 mmHg on 2 occasions 4-6 hours apart, on bedrest in hospital); pre-eclampsia (gestational hypertension + proteinuria: 1+ or 300 mg/24 hours); severe pre-eclampsia (pre-eclampsia plus 1 of BP at least 160 mmHg systolic or 110 mmHg diastolic; proteinuria at least 5 g/24 hours; oliguria < 400 mL per day; elevated liver enzymes; thrombocytopenia < 100,000/microlitre; pulmonary oedema; severe epigastric pain). Birthweight (calcium 3245 (SD 414) vs placebo 3035 (542) g); mean gestational ages (35.6 vs 34.4 weeks); 5 minute Apgar < 7 (1/29 vs 1/34); cord arterial pH (7.25 (0.07) vs 7.20 (0.07)); fetal growth impairment (2/29 vs 4/34).
Notes	Jacksonville, Florida, USA. University hospital serving low-income population Source of funding: not stated. CoI: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated list
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Tablets were prepared by a pharmaceutical company and were identical with respect to weight, size, flavour and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Tablets were prepared by a pharmaceutical company and were identical with respect to weight, size, flavour and appearance.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% attrition
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Data entered before breaking the code. ITT analysis. 4/33 in the calcium group lost to follow-up so 29 in calcium and 34 in placebo, however even if the 4 lost to follow-up had PIH, results would still have significantly favoured the calcium group.

Taherian 2002

Methods	“Healthy antepartum cases were randomized and divided into 3 groups.”
Participants	Women attending a hospital antenatal clinic in Iran between 1998 and 2001. 990 nulliparous women, single pregnancy, first prenatal visit before 20 weeks of gestation, SDP/DBP lower than 130/80 mmHg, and no proteinuria detectable by a dipstick. Participants were excluded if they had a history of cardiovascular, renal or endocrinologic problems, medical or obstetric complications; or if they had a known hazardous condition (multifetal gestation, hydatidiform mole).
Interventions	Group 1 received 75 mg aspirin each day from 20th week of pregnancy till delivery; group 2 were treated with 500 mg oral calcium-D daily (calcium-D = 500 mg calcium carbonate + 200 IU vitamin D); and the control group 3 received no medication at all.
Outcomes	Participants were considered to have mild pre-eclampsia if they demonstrated an increase of 30 mmHg in systolic or 15 mmHg in DBP above the standard pressure. In addition, they should have demonstrated equal or greater than 300 mg/24 hours in urine collection, or in 2 random urine specimens obtained 4 hours apart and containing at least 1+ protein by the dipstick method. Severe pre-eclampsia was defined as BP equal or greater than 160/110 mmHg and 4+ protein by dipstick on 2 occasions 4 hours apart.
Notes	April 1998 to March 2001. Antenatal outpatient clinics of Isfahan Health Centers Data presented as percentages with no individual n values. Have extrapolated n values from numbers and percentages given for main outcome PE (Aspirin 326, calcium 325, control 327) and calculated other numbers from percentages reported. Source of funding: Univesity Research Department. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We used a table of random number to assign each case independently to one of three groups."
Allocation concealment (selection bias)	Unclear risk	"randomly allocated to three equivalent groups."
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No record of losses to follow-up
Selective reporting (reporting bias)	Unclear risk	No information

Taherian 2002 *(Continued)*

Other bias	High risk	There was limited information on methods, and no mention of loss to follow-up.

Villar 1987

Methods	Double-blind, RCT
Participants	Recruitment 1983-1985. 34 black women from Johns Hopkins Hospital, Baltimore, USA, 18 white women from Rosario, Argentina Inclusion criteria: nulliparous or primiparous; known menstrual dates; age 18-30 years; singleton pregnancy; negative roll-over test. Exclusion criteria: underlying medical disorders. Mean calcium intake at 26 weeks was: calcium group: 1129 (SD 736) and placebo group 914 (478).
Interventions	Calcium carbonate 1.5 g (500 mg tablets) from 26 weeks' gestation vs placebo tablets. Women at Johns Hopkins Hospital also received vitamin preparations containing 200 mg calcium and 100 mg magnesium per day.
Outcomes	Weight gain in last trimester of pregnancy; BP increase; gestational hypertension
Notes	Source of funding: grants from the National Dairy Board and the National Dairy Council. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned' - no other details
Allocation concealment (selection bias)	Low risk	Random numbers in closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets were the same weight, size and colour, prepared by The Johns Hopkins pharmacy and distributed to the 2 hospitals.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Tablets were the same weight, size and colour, prepared by The Johns Hopkins pharmacy and distributed to the 2 hospitals.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% attrition
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Women at Johns Hopkins Hospital only also received vitamin preparations containing 200 mg calcium/day.

Villar 1990

Methods	Double-blind, randomised trial
Participants	Johns Hopkins Hospital, Baltimore, 1985-1988 Pregnant women 17 years or younger; no underlying medical disorders; most were nulliparous with known last menstrual period and singleton pregnancy
Interventions	2 g elemental calcium as 500 mg calcium carbonate tablets, vs placebo tablets. All women were prescribed prenatal vitamin tablets containing 200 mg calcium and 100 mg magnesium per day.
Outcomes	Preterm labour; preterm delivery < 37 weeks (calcium 7.4 vs placebo 21.1%); delivery 30-37 weeks; idiopathic prematurity; spontaneous prematurity; low birthweight (< 2500 g) (calcium 9.6% vs placebo 21.1%); postdates > 42 weeks (calcium 7.4 vs placebo 5.3%); impaired fetal growth (3.2 vs 3.2%); premature rupture of membranes (2.1 vs 1.0%); Apgar score < 8 at 5 minutes (4.4 vs 10.5%)
Notes	Source of funding: grants from the National Dairy Board and the National Dairy Council. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Low risk	Opaque envelopes with bottle numbers; project co-ordinator responsible for assigning treatment. Identical tablets and containers were prepared at The Johns Hopkins Hospital pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% attrition
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Unclear risk	Baseline characteristics similar except for maternal weight (higher in placebo group, P < 0.01)

WHO 2006

Methods	Double-blind, randomised trial. Randomisation stratified by centre, with computer-generated blocks of 6-8. Allocation by consecutively numbered treatment packs containing calcium tablets or identical placebo. Treatment packs were prepared centrally.

WHO 2006 *(Continued)*

Participants	Multicentre trial in Argentina, Egypt, India, Peru, South Africa and Vietnam. Enrolment from 2001-2003 Populations with median daily calcium intake < 600 mg; primiparous women less than 20 weeks' pregnant Exclusion criteria: renal disease or urolithiasis; parathyroid disease; BP > 140 mmHg systolic or > 90 mmHg diastolic; history of hypertension; antihypertensive therapy; diuretic, digoxin, phenytoin or tetracycline treatment
Interventions	Chewable calcium carbonate tablets with 500 mg elemental calcium, 3 daily, or identical placebo, from enrolment till delivery.
Outcomes	Primary outcomes: pre-eclampsia (BP diastolic 90 mmHg or more, or systolic 140 mmHg or more, plus proteinuria 2+ on dipsticks or 300 mg per day; preterm birth (< 37 weeks). Secondary outcomes: severe pre-eclampsia (diastolic 110 mmHg or more or systolic 160 mmHg or more); early onset pre-eclampsia (< 32 weeks), PIH; eclampsia; placental abruption; birthweight < 2500 g; spontaneous preterm delivery; medically indicated preterm delivery; admission to neonatal ICU for > 2 days; fetal, neonatal and perinatal mortality (before discharge from hospital).
Notes	Multicentre trial in Argentina, Egypt, India, Peru, South Africa and Vietnam. Enrolment from 2001-2003 14,362 women screened, 8325 randomised. Exclusions: 6 calcium (4 not pregnant, 2 lost before treatment started) and 7 placebo (5 not pregnant, 2 lost before treatment started). Loss to follow-up: 143 and 155 in calcium and placebo group respectively (some data available on women not followed up to delivery). Treatment compliance 84.5% and 86.2% respectively. Baseline characteristics were well matched. An ancillary study in Argentina assessed 510 of the participants by Doppler ultrasound for RI, PI in uterine and umbilical arteries, and for bilateral uterine artery notching (Carroli 2010). Similarly, a group of 708 participants in South Africa were assessed for serum and urine parameters of endothelial damage (Hofmeyr 2008). Source of funding: the study was supported by UNDP/UNFPA/World Health Organization/World Bank Special Programme of Research, Development and Research Training. CoI: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists for each site with random blocks of 6 to 8 women
Allocation concealment (selection bias)	Low risk	Consecutively numbered identical treatment boxes were allocated for each woman enrolled. Randomisation codes remained at the WHO Clinical Trial Unit until analysis. Boxes and tablet bottles were prepared and numbered by Magistra SA, Geneva and shipped to trial centres. The placebo and calcium tablets were identical.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Double-blind

WHO 2006 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	143/4151 and 155/4161 women in calcium and placebo groups respectively were missing delivery data but were included in other analyses.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	ITT principle. Baseline characteristics, compliance and dropout rates were similar.

ASA: acetylsalicylic acid
BMI: body mass index
BP: blood pressure
DBP: diastolic blood pressure
dl: decilitre
g: gram
GDM: gestational diabetes mellitus
ICU: intensive care unit
ITT: intention to treat
IU: international units
IUGR: intrauterine growth restriction
MAP: mean arterial pressure
mcg: microgram
mg: milligram
mmHg: millimetre of mercury
NICU: neonatal intensive care unit
PE: pulmonary embolism
PI: pulsatility index
PIH: pregnancy-induced hypertension
RCT: randomised controlled trial
RI: resistance index
SBP: systolic blood pressure
SD: standard deviation
SEM: standard error of the mean
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aghamohammady 2010	No data given in abstract. 100 nulliparous women 35 years old or more randomly allocated to receive calcium 2000 g or placebo from 15-20 weeks until term
Anu 2017	This study compared calcium supplements with traditional herbal supplements, Shatavaryadi Choorna (there was no non-active placebo).
Anumba 2006	This is a trial registration. Last entry on trial registry 2011. Reported that trial stopped and recruitment stopped
Asemi 2017	Clinical trial of the effect of multi mineral-vitamin D supplementation compared with the placebo
August 2002	Excluded pending full report of results. Inadequate data in abstracts for inclusion
Azami 2017	This was not a placebo controlled trial and the effects of calcium as part of a broader intervention was not clear. In this study there were 3 intervention groups:

Study	Reason for exclusion
	1. ferrous sulphate tablet plus multi-mineral tablet containing calcium, magnesium, zinc and D3; 2. ferrous sulphate plus vitamin E and C; 3. ferrous sulphate only.
Belizan 1983	Too little information on methods and results to include N = 36. No clinically important outcomes presented in format suitable for inclusion in this review Participants: healthy, 20-35 years, singleton pregnancy. Intervention: calcium 1 g (n = 11), calcium 2 g (n = 11) or placebo (n = 14). Outcomes: DBP 20-24 weeks, and in the third trimester. Study design: randomised, no further information.
Bhatia 2010	This is a trial registration and there is no subsequent publication although the trial is reported to be complete. Calcium was compared with calcium plus vitamin D and these groups were compared with a non-random control group.
Boggess 1997	No specified outcomes reported. Primarily a study of cardiac output measurements. Mentioned 'hypertensive complications', but do not specify what these were in the placebo group N = 23. After randomisation, 5/23 (22%) were excluded. Participants: 18-35 years. Excluded if BP > 140/90 mmHg at 24 weeks; smokers; illicit drug use; multiple pregnancy; cardiovascular renal or endocrine disease; hypertension in previous pregnancy; calcium supplementation > 200-250 mg elemental calcium Intervention: oral calcium carbonate 1.5 g/day for 6 weeks from 28-31 weeks, or placebo tablets. All had 200-250 mg calcium in standard prenatal vitamin-mineral preparations. Outcomes: gestational hypertension (BP at least 140.90 mmHg on 2 occasions, 6 hours apart); pre-eclampsia (gestational hypertension plus at least 1+ proteinuria). Study design: randomised trial; randomisation schedule in balanced blocks of 10.
Chames 2002	Excluded pending publication of full report. No relevant clinical outcomes reported in the abstract. No difference was found in blood lead levels between women receiving calcium 1000 mg daily from 13-19 weeks (n = 24) or placebo (n = 26).
Chan 2006	This is a trial registration for a study that is outside the scope of this review. The study examines dairy foods for pregnant adolescent women. The aim of the intervention is not primarily about the prevention of pre-eclampsia or hypertensive disorders.
de Souza 2006	Participants randomised to calcium 2 g/day AND aspirin (ASA)
Diogenes 2011	Supplementation with calcium (600 mg) (n = 17) plus vitamin D vs placebo (n = 9). This was a placebo controlled trial looking at calcium supplements in pregnant adolescent young women (13-19 years, mean age 17). The aim of the study was specifically looking at nutritional factors (bone mass in women and babies, etc.). The aim did not relate to hypertension and no such data are reported in any of the publications.
Dizavandy 1998	Excluded due to the unexplained large and imbalanced loss to follow-up (6/58 in calcium group and 24/85 in placebo group). Hypocalciuric women in Iran randomised to receive calcium (2 g) or identical placebo but method of randomisation is unclear. Attempts to contact authors for more details failed.
Ettinger 2011	670 women randomised to calcium 1.2 g vs placebo in first trimester of pregnancy (Mexico City, 2001-2003). Calcium was associated with reduction in bone resorption during pregnancy. The purpose of this study was not related to the prevention of hypertension.

Study	Reason for exclusion
Felix 1991	Excluded as allocation was by alternation, not random. 14 women received calcium supplementation 2 g/day and 11 received placebo. No women developed hypertension or pre-eclampsia. The production of 6-keto-prostaglandin F1alpha by umbilical arteries was similar between groups.
Fung 2010	This is a trial registration from 2010 – it has not been updated since 2013 and it is not clear whether or not the study has been completed. The aim of the study is to compare bone mass in black and white pregnant women receiving calcium supplements, starting in the 1st trimester of pregnancy. It is not about hypertension and is outside the scope of the review.
Herrera 2006a	This is a study looking at adolescent women. The aim of the study was not related to the prevention of hypertension; the study aimed to look at calcium levels 1 month after randomisation. Excluded as outside the scope of this review.
Hofmeyr 2015	This study looks at calcium supplementation before pregnancy and is therefore outside the scope of this review.
Karamali 2016	This is a placebo controlled trial recruiting women with gestational diabetes and outcomes relate to gestational diabetes (macrosomia, etc.). The intervention involved supplementation for only 6 weeks, starting at 24-28 weeks of gestation. The main focus of this study is the treatment of women with diagnosed gestational diabetes and not the prevention of hypertensive disorders so this study is outside the scope of the review.
Karandish 2003	No details of randomisation available (attempts were made to contact the author) and outcome assessed (birthweight) is not a review outcome. Study compared 1 g calcium vs placebo in 68 women from 28-30 weeks' gestation.
Kawasaki 1985	N = 94. Not a randomised trial. Interventions: calcium L-aspartate 600 mg/day from 20 weeks to delivery (n = 22) vs no supplementation (n = 72). Outcomes: pregnancy-induced hypertension.
Knight 1992	Excluded because, placebo not used, and participants not followed till delivery. Normotensive (n = 30 and hypertensive (BP 140/85 mmHg or more, n = 20) nulliparous women "randomly allocated" to receive calcium 1 g from about 12 weeks to 32 weeks, or a control group. Follow-up continued to 36 weeks. Mean DBP reduced in the hypertensive group receiving calcium.
Lavin 1986	Planned trial of calcium vs placebo in women with a positive roll-over test at 28-32 weeks. Trial was apparently cancelled.
MacDonald 1986	RCT of calcium AND vitamin D vs placebo in 55 Asian women. No method or results were provided in this personal communication from 1986. Attempts to contact the author for more details were unsuccessful.
Martin 2017	This is a dose/regime comparison looking at adherence, so is outside the scope of the review.
Montanaro 1990	N = 170. No placebo Participants: normotensive at 24 weeks' pregnancy. Interventions: calcium 2 g/day from 24 weeks to delivery. Outcomes: pregnancy-induced hypertension, pre-eclampsia. Study design: "randomised, single-blinded trial".
Mosalanejad 2016	In this trial both groups received calcium: calcium + 400 IU vitamin (usual care) plus 1000 IU D3 is compared with calcium + 400 IU vitamin D (i.e. difference between groups is the intervention group gets a large dose of vitamin D as well as usual care which includes calcium.

Study	Reason for exclusion
NCT00000543	This is a trial registration from 1999 – the women recruited already had hypertension.
Nooripour 2016	This is a trial registration looking at women with vitamin D deficiency. The intervention was vitamin D. Women in both groups received a multi-vitamin/mineral tablet containing calcium and vitamin D, women in the intervention group received an additional vitamin D supplement.
Prada 2001	Excluded pending publication of full report. Abstract does not include outcomes specified for this review. Mean BP was reduced in adolescents receiving calcium supplementation 1000 mg daily (n = 62) compared with placebo (n = 62). Not clear whether participants in this report include participants from Prada 2002
Prada 2002	Excluded pending publication of full report. Abstract does not include outcomes specified for this review. Mean BP was similar in adolescents and women with twin pregnancy receiving calcium supplementation 1000 mg daily (n = 94) compared with placebo (n = 93). Not clear whether participants in this report include participants from Prada 2001
Raman 1978	N = 273. Allocation was by strict rotation, a quasi-randomised trial. Supplementation with 300 mg vs 600 mg vs placebo. No data given on pre-eclampsia. There were biochemical data on only 87 women.
Repke 1989	N = 255. Presented as abstract only. Little information on methods and results Interventions: calcium 2 g/day vs placebo, after 20 weeks of pregnancy. Study design: "randomised clinical trial".
Roth 2014	This is a study looking at whether enteric coating enhances bioavailability of calcium and the outcomes were serum calcium soon after administration. This is outside the scope of this review. Pregnancy outcomes were not included. This was a cross-over trial which is not suitable for measuring pregnancy outcomes.
S-Ramos 1995	N = 75. Excluded because calcium was used for treatment of women with pre-eclampsia rather than prevention. Participants: nulliparous, gestation 24-36 weeks; mild pre-eclampsia (BP 140/90-160/100, proteinuria at least 300 mg/day). Interventions: calcium 2 g/day elemental calcium (4 tablets of calcium carbonate 1250 mg), vs matching placebo. Outcomes: initial and last BP and biochemical markers; preterm delivery; caesarean section; severe pre-eclampsia; gestation at delivery; birthweight; Apgar < 7 at 1 minute and 5 minutes; cord arterial pH < 7.16; fetal growth restriction; perinatal death. Study design: double-blind, placebo-controlled study using a computer-generated random number list.
Salzano 2001	Method of "randomisation" not described and no explanation given for discrepancy in group sizes (25 vs 40).
Samimi 2016	N = 60. This study examined high-dose calcium supplements (1 g) plus vitamin D. High-dose supplements with additional vitamins or minerals are outside the scope of this review.
Souza 2014	This study looked at women receiving aspirin plus calcium vs placebo. Women had chronic hypertension. The intervention was a combined intervention; the effect of calcium alone would not be apparent.
Subprabha 2017	Trial registration. This is not a placebo controlled trial; rather, it looks at a traditional treatment vs calcium supplements.
Suzuki 1996	N = 152. Not a randomised trial

Study	Reason for exclusion
	Interventions: calcium 1 g/day from 20 weeks vs no calcium. Outcomes: pre-eclampsia, gestational hypertension.
Tamas 1997	Study of treatment of gestational hypertension, not prevention, using the drug dobesilate calcium, not calcium supplementation.
Wanchu 2001	No placebo used. 120 consecutive nulliparous women less than 20 weeks' pregnant "randomly assigned" to receive 2 g elemental calcium daily, or no treatment. Analysis restricted to 100 women who "completed the protocol". Mild pre-eclampsia occurred in 9/50 vs 6/50 and severe pre-eclampsia in 0/50 vs 2/50 study vs control groups respectively.
Zheng 2000	This was not a placebo controlled trial.

ASA: acetylsalicylic acid
BP: blood pressure
DBP: diastolic blood pressure
g: gram
IU: international units
mg: milligram
mmHg: millimetre of mercury
RCT: randomised controlled trial
vs: versus

Characteristics of studies awaiting assessment *[ordered by study ID]*

Liu 2013

Methods	Randomised controlled trial
Participants	Inclusion criteria: nulliparity; age ≥ 35 years; previous pre-eclampsia; family history of pre-eclampsia; multiple pregnancy; time between pregnancies ≥ 10 years; body mass index ≥ 25; diastolic pressure ≥ 80 mmHg before 20 weeks' gestation; proteinuria ≥+ on more than 1 occasion or ≥ 300 mg/24 h before 20 weeks' gestation; underlying medical conditions (pre-existing hypertension; pre-existing renal disease; pre-existing diabetes; presence of antiphospholipid antibodies; chronic autoimmune disease); male sex partner's predecessor wife has previous pre-eclampsia. The inclusion criteria include women who already have hypertension, but it may be that women that are actually recruited may not have these specific risk factors.
Interventions	This is a calcium supplement dose comparison 600 mg versus 1200 mg; it is not a placebo controlled trial.
Outcomes	Pre-eclampsia.
Notes	This is a trial registration — the study is specifically about prevention of pre-eclampsia — recruitment should have ended (2015) but there are no subsequent updates of the registration or publications. Awaiting assessment pending further publications.

mg: milligram
mmHg: millimetre of mercury

Characteristics of ongoing studies *[ordered by study ID]*

Chaiarach 2017

Trial name or title	Combined therapy with low-dose aspirin and calcium supplements during second trimester to reduce the risk of superimposed pre-eclampsia in pregnant women with chronic hypertension: a randomised-controlled trial
Methods	Placebo controlled randomised trial
Participants	104 women with chronic hypertension Inclusion criteria 1. Pregnant woman with chronic hypertension aged 20 years or more 2. Attending antenatal care and planning to delivery at Khon Kaen Hospital and Srinagarind Hospital 3. Carrying a live structurally normal singleton fetus between 13 to16 weeks of gestation 4. Participants give informed consent Exclusion criteria 1. History of bleeding disorders 2. Thrombocytopenia platelet count 140,000 mm3 3. Placenta previa 4. Asthma 5. Allergy to aspirin 6. Planning to delivery in other hospitals
Interventions	Low-dose aspirin (81 mg) and calcium carbonate 1500 mg per day compared with placebo
Outcomes	Pre-eclampsia, neonatal outcomes
Starting date	01 July 2017 (anticipated). Reported completion date: 31 May 2018.
Contact information	Sukanya Chaiarach, sukanyatanoorat@hotmail.com
Notes	

Mahomed 1998

Trial name or title	Calcium supplementation for the prevention of pregnancy-induced hypertension and preterm labour in twin pregnancies
Methods	Randomised controlled trial
Participants	Women with twin pregnancy
Interventions	Calcium solution (1 g elemental calcium per 5 mL).
Outcomes	Pregnancy-induced hypertension, preterm labour, perinatal mortality and short-term morbidity, maternal morbidity
Starting date	Not stated
Contact information	Prof K Mahomed
Notes	Sample size 400 per group

Sulovic 2013

Trial name or title	Did calcium management prevent pre-eclampsia?
Methods	Randomised controlled trial
Participants	9178 healthy nulliparous woman 14-23 weeks' gestation
Interventions	2 g calcium vs placebo until the end of pregnancy
Outcomes	Pre-eclampsia, preterm birth
Starting date	Not clear
Contact information	Belgrade University (no email)
Notes	(Reported in abstract.) Although this study appears to have been completed we are awaiting publication of full trial results. There was insufficient information to assess risk of bias and extract data.

Torloni 2015

Trial name or title	Low dose calcium to prevent pre-eclampsia (AMCAL)
Methods	Randomised controlled trial
Participants	1040 women 16-20 weeks' gestation
Interventions	Dietary supplement: calcium: 1 chewable tablet daily, at bedtime, containing 500 mg elemental calcium (1250 mg calcium carbonate) plus educational sessions (women will participate in at least 2 interactive group educational sessions lasting 30 minutes each; session content to include importance of calcium during pregnancy and how to modify their diets to include calcium-rich foods that are available locally) versus educational sessions alone.
Outcomes	Pre-eclampsia, hypertensive disorders of pregnancy. Change in dietary calcium intake, hospital admission for hypertension, maternal mortality, severe maternal morbidity (eclampsia, HELLP), side effects, preterm birth, neonatal outcomes
Starting date	October 2014 (estimated completion October 2016)
Contact information	Professor da Silva Moura Souza, celsa22@hotmail.com
Notes	Last updated Feb 2016, still recruiting

g: gram
mg: milligram
mL: millilitre
vs: versus

DATA AND ANALYSES

Comparison 1. Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium

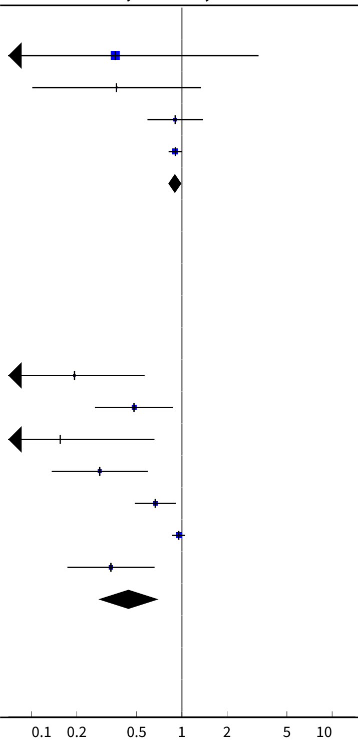
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without proteinuria)	12	15470	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.81]
1.1 Adequate calcium diet	4	5022	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
1.2 Low calcium diet	7	10418	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.70]
1.3 Dietary calcium not specified	1	30	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.45]
2 Pre-eclampsia	13	15730	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.31, 0.65]
2.1 Adequate calcium diet	4	5022	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.20]
2.2 Low calcium diet	8	10678	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.20, 0.65]
2.3 Dietary calcium not specified	1	30	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.02]
3 Preterm birth	11	15275	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
3.1 Adequate calcium diet	4	5033	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.26, 1.33]
3.2 Low calcium diet	7	10242	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.02]
4 Admission to neonatal intensive care unit	4	13406	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
4.1 Adequate calcium diet	1	4336	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.95, 1.26]
4.2 Low calcium diet	3	9070	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.19]
5 Stillbirth or death before discharge from hospital	11	15665	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.09]
5.1 Adequate calcium diet	4	5033	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.66, 1.90]
5.2 Low calcium diet	7	10632	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.07]
6 Maternal death/serious morbidity	4	9732	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.98]
6.1 Low calcium diet	4	9732	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.98]
6.2 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Placental abruption	5	14336	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.34]
7.1 Adequate calcium diet	3	4830	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.39, 1.68]
7.2 Low calcium diet	2	9506	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.51, 1.55]
8 Caesarean section	8	15234	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Adequate calcium diet	3	4981	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
8.2 Low calcium diet	5	10253	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.88, 1.04]
9 Proteinuria (gestational with no proteinuria)	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.26]
9.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.26]
10 Severe pre-eclampsia	1	8302	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.15]
10.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Low calcium diet	1	8302	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.15]
11 Eclampsia	3	13425	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.41, 1.27]
11.1 Adequate calcium diet	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.25, 3.99]
11.2 Low calcium diet	2	8836	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.37, 1.26]
12 HELLP syndrome	2	12901	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.05, 6.82]
12.1 Adequate calcium diet	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.73, 16.82]
12.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.70, 7.32]
13 Intensive care unit admission	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
13.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
14 Maternal death	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.39]
14.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.39]
15 Low birthweight (birthweight < 2500 g)	9	14883	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
15.1 Adequate calcium diet	4	5033	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.31, 1.13]
15.2 Low calcium diet	5	9850	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.05]
16 Neonate small-for-gestational age as defined by trial authors	4	13615	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.29]
16.1 Adequate calcium diet	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.92, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Low calcium diet	3	9026	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.21]
17 Systolic blood pressure > 95th percentile during childhood	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.91]
17.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Low calcium diet	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.91]
18 Diastolic blood pressure > 95th percentile during childhood	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]
18.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Low calcium diet	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]
19 Dental caries in childhood	1	195	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.87]
19.1 Low calcium diet	1	195	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.87]

Analysis 1.1. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 1 High blood pressure (with or without proteinuria).

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Adequate calcium diet					
Villar 1987	1/25	3/27		0.89%	0.36[0.04,3.24]
Villar 1990	3/90	8/88		2.36%	0.37[0.1,1.34]
Crowther 1999	34/227	38/229		10.9%	0.9[0.59,1.38]
CPEP 1997	509/2163	565/2173		18.53%	0.91[0.82,1]
Subtotal (95% CI)	**2505**	**2517**		**32.67%**	**0.9[0.81,0.99]**
Total events: 547 (Calcium), 614 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.53, df=3(P=0.47); I²=0%					
Test for overall effect: Z=2.09(P=0.04)					
1.1.2 Low calcium diet					
L-Jaramillo 1990	3/22	24/34		3.24%	0.19[0.07,0.57]
S-Ramos 1994	9/29	22/34		7.64%	0.48[0.26,0.87]
L-Jaramillo 1989	2/55	12/51		1.93%	0.15[0.04,0.66]
Purwar 1996	8/97	27/93		5.81%	0.28[0.14,0.59]
Belizan 1991	57/579	87/588		13.61%	0.67[0.49,0.91]
WHO 2006	613/4151	645/4161		18.56%	0.95[0.86,1.05]
Kumar 2009	11/273	30/251		6.61%	0.34[0.17,0.66]
Subtotal (95% CI)	**5206**	**5212**		**57.41%**	**0.44[0.28,0.7]**
Total events: 703 (Calcium), 847 (Placebo)					
Heterogeneity: Tau²=0.26; Chi²=39.35, df=6(P<0.0001); I²=84.75%					
Test for overall effect: Z=3.48(P=0)					



Favours calcium | Favours placebo

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.3 Dietary calcium not specified					
Niromanesh 2001	10/15	11/15		9.92%	0.91[0.57,1.45]
Subtotal (95% CI)	**15**	**15**		**9.92%**	**0.91[0.57,1.45]**
Total events: 10 (Calcium), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
Total (95% CI)	**7726**	**7744**		**100%**	**0.65[0.53,0.81]**
Total events: 1260 (Calcium), 1472 (Placebo)					
Heterogeneity: Tau^2=0.06; Chi^2=42.4, df=11(P<0.0001); I^2=74.06%					
Test for overall effect: Z=3.95(P<0.0001)					
Test for subgroup differences: Chi^2=8.78, df=1 (P=0.01), I^2=77.22%					
	Favours calcium		0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 1.2. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 2 Pre-eclampsia.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Adequate calcium diet					
Villar 1987	1/25	3/27		2.41%	0.36[0.04,3.24]
Villar 1990	0/90	3/88		1.42%	0.14[0.01,2.67]
Crowther 1999	10/227	23/229		10.6%	0.44[0.21,0.9]
CPEP 1997	158/2163	168/2173		16.91%	0.94[0.77,1.16]
Subtotal (95% CI)	**2505**	**2517**		**31.34%**	**0.62[0.32,1.2]**
Total events: 169 (Calcium), 197 (Placebo)					
Heterogeneity: Tau^2=0.2; Chi^2=6.2, df=3(P=0.1); I^2=51.58%					
Test for overall effect: Z=1.43(P=0.15)					
1.2.2 Low calcium diet					
L-Jaramillo 1990	0/22	8/34		1.56%	0.09[0.01,1.48]
S-Ramos 1994	4/29	15/34		7.81%	0.31[0.12,0.84]
L-Jaramillo 1989	2/55	12/51		4.72%	0.15[0.04,0.66]
Purwar 1996	2/97	11/93		4.57%	0.17[0.04,0.77]
L-Jaramillo 1997	4/125	21/135		7.33%	0.21[0.07,0.58]
Belizan 1991	15/579	23/588		11.58%	0.66[0.35,1.26]
WHO 2006	171/4151	186/4161		16.96%	0.92[0.75,1.13]
Kumar 2009	11/273	30/251		11.21%	0.34[0.17,0.66]
Subtotal (95% CI)	**5331**	**5347**		**65.75%**	**0.36[0.2,0.65]**
Total events: 209 (Calcium), 306 (Placebo)					
Heterogeneity: Tau^2=0.44; Chi^2=29.35, df=7(P=0); I^2=76.15%					
Test for overall effect: Z=3.4(P=0)					
1.2.3 Dietary calcium not specified					
Niromanesh 2001	1/15	7/15		2.91%	0.14[0.02,1.02]
Subtotal (95% CI)	**15**	**15**		**2.91%**	**0.14[0.02,1.02]**
Total events: 1 (Calcium), 7 (Placebo)					
Heterogeneity: Not applicable					
	Favours calcium		0.001 0.1 1 10 1000	Favours placebo	

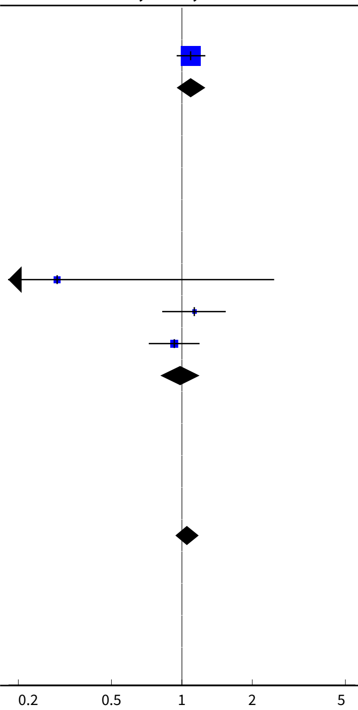
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.94(P=0.05)					
Total (95% CI)	**7851**	**7879**		**100%**	**0.45[0.31,0.65]**
Total events: 379 (Calcium), 510 (Placebo)					
Heterogeneity: Tau²=0.2; Chi²=40.31, df=12(P<0.0001); I²=70.23%					
Test for overall effect: Z=4.29(P<0.0001)					
Test for subgroup differences: Chi²=2.73, df=1 (P=0.26), I²=26.76%					
	Favours calcium		0.001 0.1 1 10 1000	Favours placebo	

Analysis 1.3. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 3 Preterm birth.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Adequate calcium diet					
Villar 1987	0/25	0/27			Not estimable
Villar 1990	7/94	20/95		6.57%	0.35[0.16,0.8]
Crowther 1999	10/227	23/229		7.89%	0.44[0.21,0.9]
CPEP 1997	248/2163	229/2173		25.49%	1.09[0.92,1.29]
Subtotal (95% CI)	**2509**	**2524**		**39.94%**	**0.59[0.26,1.33]**
Total events: 265 (Calcium), 272 (Placebo)					
Heterogeneity: Tau²=0.42; Chi²=12.31, df=2(P=0); I²=83.75%					
Test for overall effect: Z=1.26(P=0.21)					
1.3.2 Low calcium diet					
L-Jaramillo 1990	0/22	4/34		0.66%	0.17[0.01,2.99]
S-Ramos 1994	5/29	8/34		4.68%	0.73[0.27,1.99]
Purwar 1996	2/97	6/93		2.09%	0.32[0.07,1.54]
L-Jaramillo 1997	0/125	0/135			Not estimable
Belizan 1991	33/527	37/542		14.09%	0.92[0.58,1.44]
WHO 2006	398/4038	436/4042		26.99%	0.91[0.8,1.04]
Kumar 2009	19/273	32/251		11.55%	0.55[0.32,0.94]
Subtotal (95% CI)	**5111**	**5131**		**60.06%**	**0.81[0.64,1.02]**
Total events: 457 (Calcium), 523 (Placebo)					
Heterogeneity: Tau²=0.02; Chi²=6.34, df=5(P=0.27); I²=21.16%					
Test for overall effect: Z=1.76(P=0.08)					
Total (95% CI)	**7620**	**7655**		**100%**	**0.76[0.6,0.97]**
Total events: 722 (Calcium), 795 (Placebo)					
Heterogeneity: Tau²=0.05; Chi²=20.04, df=8(P=0.01); I²=60.07%					
Test for overall effect: Z=2.23(P=0.03)					
Test for subgroup differences: Chi²=0.53, df=1 (P=0.47), I²=0%					
	Favours calcium		0.5 0.7 1 1.5 2	Favours placebo	

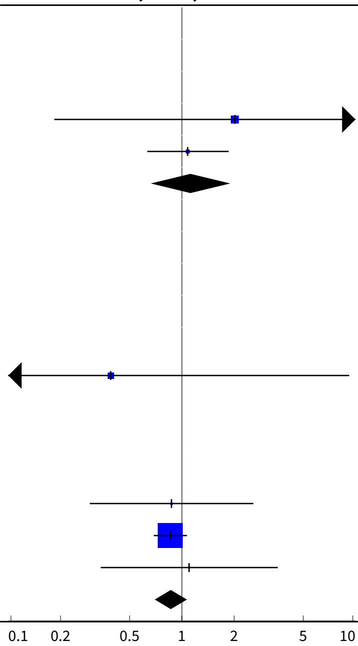
Analysis 1.4. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 4 Admission to neonatal intensive care unit.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Adequate calcium diet					
CPEP 1997	343/2163	315/2173		62.19%	1.09[0.95,1.26]
Subtotal (95% CI)	**2163**	**2173**		**62.19%**	**1.09[0.95,1.26]**
Total events: 343 (Calcium), 315 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					
1.4.2 Low calcium diet					
S-Ramos 1994	1/29	4/34		0.73%	0.29[0.03,2.48]
Belizan 1991	72/544	65/554		12.75%	1.13[0.82,1.54]
WHO 2006	114/3953	123/3956		24.33%	0.93[0.72,1.19]
Subtotal (95% CI)	**4526**	**4544**		**37.81%**	**0.98[0.81,1.19]**
Total events: 187 (Calcium), 192 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.18$, df=2(P=0.34); $I^2=8.24\%$					
Test for overall effect: Z=0.17(P=0.86)					
Total (95% CI)	**6689**	**6717**		**100%**	**1.05[0.94,1.18]**
Total events: 530 (Calcium), 507 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.83$, df=3(P=0.42); $I^2=0\%$					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: $Chi^2=0.76$, df=1 (P=0.38), $I^2=0\%$					

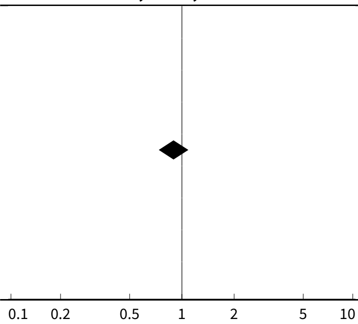


Analysis 1.5. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 5 Stillbirth or death before discharge from hospital.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Adequate calcium diet					
Villar 1987	0/25	0/27			Not estimable
Villar 1990	0/94	0/95			Not estimable
Crowther 1999	2/227	1/229		0.49%	2.02[0.18,22.09]
CPEP 1997	27/2163	25/2173		12.16%	1.08[0.63,1.86]
Subtotal (95% CI)	**2509**	**2524**		**12.64%**	**1.12[0.66,1.9]**
Total events: 29 (Calcium), 26 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.25$, df=1(P=0.62); $I^2=0\%$					
Test for overall effect: Z=0.42(P=0.67)					
1.5.2 Low calcium diet					
S-Ramos 1994	0/29	1/34		0.67%	0.39[0.02,9.2]
L-Jaramillo 1989	0/49	0/43			Not estimable
Purwar 1996	0/97	0/93			Not estimable
L-Jaramillo 1997	0/125	0/135			Not estimable
Belizan 1991	6/558	7/567		3.38%	0.87[0.29,2.58]
WHO 2006	142/4181	166/4197		80.76%	0.86[0.69,1.07]
Kumar 2009	6/273	5/251		2.54%	1.1[0.34,3.57]
Subtotal (95% CI)	**5312**	**5320**		**87.36%**	**0.86[0.7,1.07]**



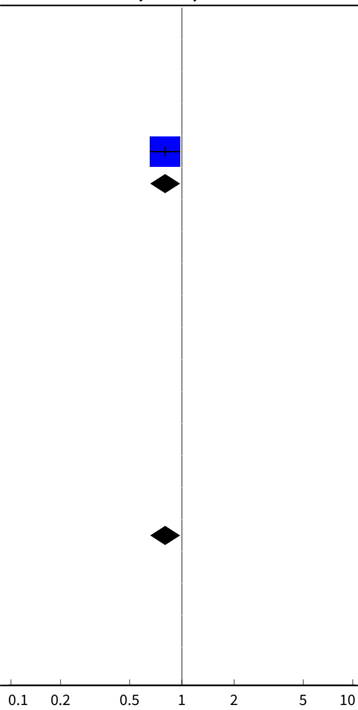
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 154 (Calcium), 179 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.41, df=3(P=0.94); I²=0%					
Test for overall effect: Z=1.37(P=0.17)					
Total (95% CI)	**7821**	**7844**		**100%**	**0.9[0.74,1.09]**
Total events: 183 (Calcium), 205 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.46, df=5(P=0.92); I²=0%					
Test for overall effect: Z=1.11(P=0.27)					
Test for subgroup differences: Chi²=0.82, df=1 (P=0.37), I²=0%					



Favours calcium — Favours placebo

Analysis 1.6. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 6 Maternal death/serious morbidity.

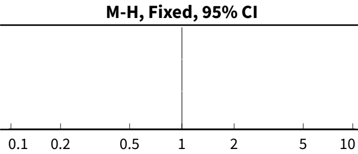
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Low calcium diet					
S-Ramos 1994	0/29	0/34			Not estimable
Purwar 1996	0/97	0/93			Not estimable
Belizan 1991	0/579	0/588			Not estimable
WHO 2006	167/4151	209/4161		100%	0.8[0.66,0.98]
Subtotal (95% CI)	**4856**	**4876**		**100%**	**0.8[0.66,0.98]**
Total events: 167 (Calcium), 209 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.19(P=0.03)					
1.6.2 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**4856**	**4876**		**100%**	**0.8[0.66,0.98]**
Total events: 167 (Calcium), 209 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.19(P=0.03)					
Test for subgroup differences: Not applicable					



Favours calcium — Favours placebo

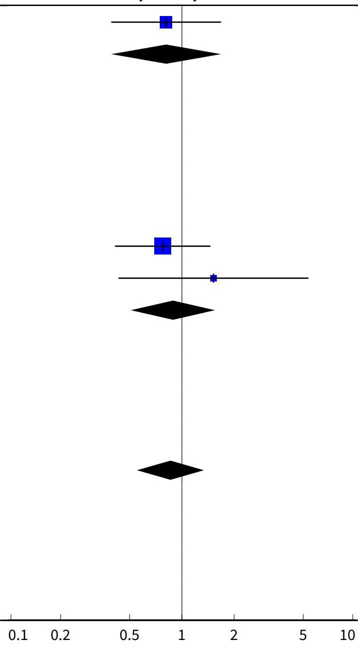
Analysis 1.7. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 7 Placental abruption.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Adequate calcium diet					
Villar 1987	0/25	0/27			Not estimable
Villar 1990	0/94	0/95			Not estimable



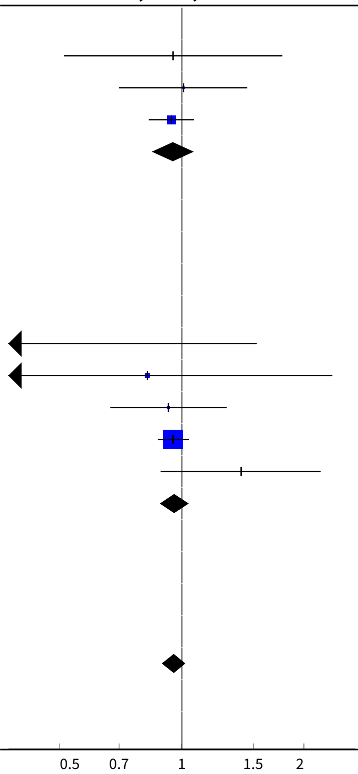
Favours calcium — Favours placebo

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
CPEP 1997	13/2295	16/2294		38.15%	0.81[0.39,1.68]
Subtotal (95% CI)	**2414**	**2416**		**38.15%**	**0.81[0.39,1.68]**
Total events: 13 (Calcium), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.58)					
1.7.2 Low calcium diet					
WHO 2006	17/4151	22/4161		52.38%	0.77[0.41,1.46]
Belizan 1991	6/593	4/601		9.47%	1.52[0.43,5.36]
Subtotal (95% CI)	**4744**	**4762**		**61.85%**	**0.89[0.51,1.55]**
Total events: 23 (Calcium), 26 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
Total (95% CI)	**7158**	**7178**		**100%**	**0.86[0.55,1.34]**
Total events: 36 (Calcium), 42 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.85), I^2=0%					



Analysis 1.8. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 8 Caesarean section.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Adequate calcium diet					
Villar 1990	16/94	17/95		1.2%	0.95[0.51,1.77]
Crowther 1999	46/227	46/229		3.25%	1.01[0.7,1.45]
CPEP 1997	366/2163	390/2173		27.59%	0.94[0.83,1.07]
Subtotal (95% CI)	**2484**	**2497**		**32.03%**	**0.95[0.84,1.07]**
Total events: 428 (Calcium), 453 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=2(P=0.94); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					
1.8.2 Low calcium diet					
S-Ramos 1994	1/29	6/34		0.39%	0.2[0.02,1.53]
Purwar 1996	6/97	7/93		0.51%	0.82[0.29,2.35]
Belizan 1991	60/544	66/554		4.64%	0.93[0.67,1.29]
WHO 2006	809/4181	854/4197		60.44%	0.95[0.87,1.04]
Kumar 2009	41/273	27/251		1.99%	1.4[0.89,2.2]
Subtotal (95% CI)	**5124**	**5129**		**67.97%**	**0.96[0.88,1.04]**
Total events: 917 (Calcium), 960 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.08, df=4(P=0.28); I^2=21.28%					
Test for overall effect: Z=1.06(P=0.29)					
Total (95% CI)	**7608**	**7626**		**100%**	**0.95[0.89,1.02]**
Total events: 1345 (Calcium), 1413 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.21, df=7(P=0.63); I^2=0%					



Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.35(P=0.18)					
Test for subgroup differences: Chi²=0.01, df=1 (P=0.92), I²=0%					
		Favours calcium	0.5 0.7 1 1.5 2	Favours placebo	

Analysis 1.9. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 9 Proteinuria (gestational with no proteinuria).

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.9.2 Low calcium diet					
WHO 2006	201/4151	194/4161		100%	1.04[0.86,1.26]
Subtotal (95% CI)	**4151**	**4161**		**100%**	**1.04[0.86,1.26]**
Total events: 201 (Calcium), 194 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
Total (95% CI)	**4151**	**4161**		**100%**	**1.04[0.86,1.26]**
Total events: 201 (Calcium), 194 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
Test for subgroup differences: Not applicable					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 1.10. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 10 Severe pre-eclampsia.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.10.2 Low calcium diet					
WHO 2006	35/4151	47/4151		100%	0.74[0.48,1.15]
Subtotal (95% CI)	**4151**	**4151**		**100%**	**0.74[0.48,1.15]**
Total events: 35 (Calcium), 47 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**4151**	**4151**		**100%**	**0.74[0.48,1.15]**
Total events: 35 (Calcium), 47 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					
Test for subgroup differences: Not applicable					

Favours calcium 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 1.11. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 11 Eclampsia.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Adequate calcium diet					
CPEP 1997	4/2295	4/2294		13.81%	1[0.25,3.99]
Subtotal (95% CI)	**2295**	**2294**		**13.81%**	**1[0.25,3.99]**
Total events: 4 (Calcium), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0(P=1)					
1.11.2 Low calcium diet					
WHO 2006	17/4151	25/4161		86.19%	0.68[0.37,1.26]
Kumar 2009	0/273	0/251			Not estimable
Subtotal (95% CI)	**4424**	**4412**		**86.19%**	**0.68[0.37,1.26]**
Total events: 17 (Calcium), 25 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=1.22(P=0.22)					
Total (95% CI)	**6719**	**6706**		**100%**	**0.73[0.41,1.27]**
Total events: 21 (Calcium), 29 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.25, df=1(P=0.62); I²=0%					
Test for overall effect: Z=1.12(P=0.26)					
Test for subgroup differences: Chi²=0.25, df=1 (P=0.62), I²=0%					

Favours calcium 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 1.12. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 12 HELLP syndrome.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 Adequate calcium diet					
CPEP 1997	7/2295	2/2294		33.36%	3.5[0.73,16.82]
Subtotal (95% CI)	**2295**	**2294**		**33.36%**	**3.5[0.73,16.82]**
Total events: 7 (Calcium), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.56(P=0.12)					
1.12.2 Low calcium diet					

Favours calcium 0.01 0.1 1 10 100 Favours placebo

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHO 2006	9/4151	4/4161		66.64%	2.26[0.7,7.32]
Subtotal (95% CI)	**4151**	**4161**		**66.64%**	**2.26[0.7,7.32]**
Total events: 9 (Calcium), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.35(P=0.18)					
Total (95% CI)	**6446**	**6455**		**100%**	**2.67[1.05,6.82]**
Total events: 16 (Calcium), 6 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.66); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi²=0.19, df=1 (P=0.66), I²=0%					
		Favours calcium	0.01 0.1 1 10 100	Favours placebo	

Analysis 1.13. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 13 Intensive care unit admission.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.13.2 Low calcium diet					
WHO 2006	116/4151	138/4161		100%	0.84[0.66,1.07]
Subtotal (95% CI)	**4151**	**4161**		**100%**	**0.84[0.66,1.07]**
Total events: 116 (Calcium), 138 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					
Total (95% CI)	**4151**	**4161**		**100%**	**0.84[0.66,1.07]**
Total events: 116 (Calcium), 138 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					
Test for subgroup differences: Not applicable					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 1.14. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 14 Maternal death.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
		Favours calcium	0.01 0.1 1 10 100	Favours placebo	

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					
1.14.2 Low calcium diet					
WHO 2006	1/4151	6/4161		100%	0.17[0.02,1.39]
Subtotal (95% CI)	**4151**	**4161**		**100%**	**0.17[0.02,1.39]**
Total events: 1 (Calcium), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
Total (95% CI)	**4151**	**4161**		**100%**	**0.17[0.02,1.39]**
Total events: 1 (Calcium), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
Test for subgroup differences: Not applicable					

Favours calcium 0.01 0.1 1 10 100 Favours placebo

Analysis 1.15. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 15 Low birthweight (birthweight < 2500 g).

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Adequate calcium diet					
Villar 1987	0/25	0/27			Not estimable
Villar 1990	9/94	20/95		4.8%	0.45[0.22,0.95]
Crowther 1999	6/227	17/229		3.24%	0.36[0.14,0.89]
CPEP 1997	188/2163	205/2173		27.5%	0.92[0.76,1.11]
Subtotal (95% CI)	**2509**	**2524**		**35.54%**	**0.59[0.31,1.13]**
Total events: 203 (Calcium), 242 (Placebo)					
Heterogeneity: Tau^2=0.23; Chi^2=7, df=2(P=0.03); I^2=71.43%					
Test for overall effect: Z=1.58(P=0.11)					
1.15.2 Low calcium diet					
L-Jaramillo 1989	0/49	0/43			Not estimable
L-Jaramillo 1997	0/125	0/135			Not estimable
Belizan 1991	31/547	41/559		10.65%	0.77[0.49,1.21]
WHO 2006	512/3930	524/3938		35%	0.98[0.87,1.1]
Kumar 2009	64/273	71/251		18.81%	0.83[0.62,1.11]
Subtotal (95% CI)	**4924**	**4926**		**64.46%**	**0.95[0.85,1.05]**
Total events: 607 (Calcium), 636 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=1.03(P=0.3)					
Total (95% CI)	**7433**	**7450**		**100%**	**0.85[0.72,1.01]**
Total events: 810 (Calcium), 878 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=9.93, df=5(P=0.08); I^2=49.65%					
Test for overall effect: Z=1.88(P=0.06)					
Test for subgroup differences: Chi^2=1.97, df=1 (P=0.16), I^2=49.18%					

Favours calcium 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 1.16. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 16 Neonate small-for-gestational age as defined by trial authors.

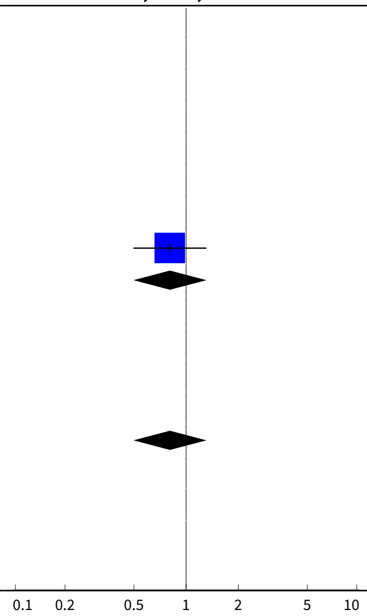
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Adequate calcium diet					
CPEP 1997	124/2295	105/2294		61.41%	1.18[0.92,1.52]
Subtotal (95% CI)	**2295**	**2294**		**61.41%**	**1.18[0.92,1.52]**
Total events: 124 (Calcium), 105 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					
1.16.2 Low calcium diet					
Kumar 2009	17/273	21/251		12.79%	0.74[0.4,1.38]
Purwar 1996	6/97	8/93		4.78%	0.72[0.26,1.99]
WHO 2006	34/4151	36/4161		21.02%	0.95[0.59,1.51]
Subtotal (95% CI)	**4521**	**4505**		**38.59%**	**0.85[0.6,1.21]**
Total events: 57 (Calcium), 65 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.49, df=2(P=0.78); I²=0%					
Test for overall effect: Z=0.9(P=0.37)					
Total (95% CI)	**6816**	**6799**		**100%**	**1.05[0.86,1.29]**
Total events: 181 (Calcium), 170 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.74, df=3(P=0.43); I²=0%					
Test for overall effect: Z=0.5(P=0.62)					
Test for subgroup differences: Chi²=2.2, df=1 (P=0.14), I²=54.64%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 1.17. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 17 Systolic blood pressure > 95th percentile during childhood.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.17.2 Low calcium diet					
Belizan 1991	29/254	50/260		100%	0.59[0.39,0.91]
Subtotal (95% CI)	**254**	**260**		**100%**	**0.59[0.39,0.91]**
Total events: 29 (Calcium), 50 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.41(P=0.02)					
Total (95% CI)	**254**	**260**		**100%**	**0.59[0.39,0.91]**
Total events: 29 (Calcium), 50 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.41(P=0.02)					
Test for subgroup differences: Not applicable					
		Favours calcium	0.01 0.1 1 10 100	Favours placebo	

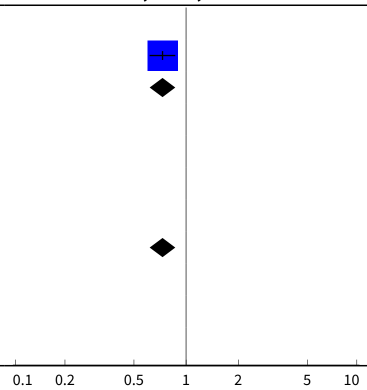
Analysis 1.18. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 18 Diastolic blood pressure > 95th percentile during childhood.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.18.2 Low calcium diet					
Belizan 1991	26/254	33/260		100%	0.81[0.5,1.31]
Subtotal (95% CI)	**254**	**260**		**100%**	**0.81[0.5,1.31]**
Total events: 26 (Calcium), 33 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.38)					
Total (95% CI)	**254**	**260**		**100%**	**0.81[0.5,1.31]**
Total events: 26 (Calcium), 33 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: Not applicable					



Analysis 1.19. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 19 Dental caries in childhood.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.19.1 Low calcium diet					
Belizan 1991	62/98	84/97		100%	0.73[0.62,0.87]
Subtotal (95% CI)	**98**	**97**		**100%**	**0.73[0.62,0.87]**
Total events: 62 (Calcium), 84 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.62(P=0)					
Total (95% CI)	**98**	**97**		**100%**	**0.73[0.62,0.87]**
Total events: 62 (Calcium), 84 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.62(P=0)					

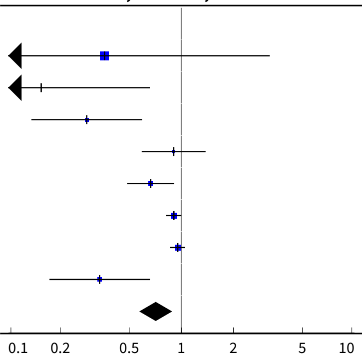


Comparison 2. Routine high-dose calcium supplementation in pregnancy by hypertension risk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without proteinuria)	12	15470	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.81]
1.1 Low-risk women	8	15143	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.57, 0.89]
1.2 High-risk women	4	327	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 0.97]
2 Pre-eclampsia	13	15730	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.31, 0.65]
2.1 Low-risk women	8	15143	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.41, 0.83]
2.2 High-risk women	5	587	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.12, 0.42]
3 Preterm birth	11	15275	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
3.1 Low-risk women	7	14707	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.67, 1.05]
3.2 High-risk women	4	568	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.24, 0.83]
4 Admission to neonatal intensive care unit	4	13406	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
4.1 Low-risk women	3	13343	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.19]
4.2 High-risk women	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.03, 2.48]
5 Stillbirth or death before discharge from hospital	11	15665	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.09]
5.1 Low-risk women	8	15153	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.09]
5.2 High-risk women	3	512	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 9.20]

Analysis 2.1. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 1 High blood pressure (with or without proteinuria).

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Low-risk women					
Villar 1987	1/25	3/27		0.89%	0.36[0.04,3.24]
L-Jaramillo 1989	2/55	12/51		1.93%	0.15[0.04,0.66]
Purwar 1996	8/97	27/93		5.81%	0.28[0.14,0.59]
Crowther 1999	34/227	38/229		10.9%	0.9[0.59,1.38]
Belizan 1991	57/579	87/588		13.61%	0.67[0.49,0.91]
CPEP 1997	509/2163	565/2173		18.53%	0.91[0.82,1]
WHO 2006	613/4151	645/4161		18.56%	0.95[0.86,1.05]
Kumar 2009	11/273	30/251		6.61%	0.34[0.17,0.66]
Subtotal (95% CI)	**7570**	**7573**		**76.84%**	**0.71[0.57,0.89]**



Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 1235 (Calcium), 1407 (Placebo)					
Heterogeneity: Tau²=0.05; Chi²=28.83, df=7(P=0); I²=75.72%					
Test for overall effect: Z=3.05(P=0)					
2.1.2 High-risk women					
Niromanesh 2001	10/15	11/15		9.92%	0.91[0.57,1.45]
L-Jaramillo 1990	3/22	24/34		3.24%	0.19[0.07,0.57]
S-Ramos 1994	9/29	22/34		7.64%	0.48[0.26,0.87]
Villar 1990	3/90	8/88		2.36%	0.37[0.1,1.34]
Subtotal (95% CI)	**156**	**171**		**23.16%**	**0.47[0.22,0.97]**
Total events: 25 (Calcium), 65 (Placebo)					
Heterogeneity: Tau²=0.38; Chi²=11.01, df=3(P=0.01); I²=72.76%					
Test for overall effect: Z=2.03(P=0.04)					
Total (95% CI)	**7726**	**7744**		**100%**	**0.65[0.53,0.81]**
Total events: 1260 (Calcium), 1472 (Placebo)					
Heterogeneity: Tau²=0.06; Chi²=42.4, df=11(P<0.0001); I²=74.06%					
Test for overall effect: Z=3.95(P<0.0001)					
Test for subgroup differences: Chi²=1.16, df=1 (P=0.28), I²=13.77%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 2.2. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 2 Pre-eclampsia.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Low-risk women					
Villar 1987	1/25	3/27		2.41%	0.36[0.04,3.24]
L-Jaramillo 1989	2/55	12/51		4.72%	0.15[0.04,0.66]
Purwar 1996	2/97	11/93		4.57%	0.17[0.04,0.77]
Crowther 1999	10/227	23/229		10.6%	0.44[0.21,0.9]
Belizan 1991	15/579	23/588		11.58%	0.66[0.35,1.26]
CPEP 1997	158/2163	168/2173		16.91%	0.94[0.77,1.16]
WHO 2006	171/4151	186/4161		16.96%	0.92[0.75,1.13]
Kumar 2009	11/273	30/251		11.21%	0.34[0.17,0.66]
Subtotal (95% CI)	**7570**	**7573**		**78.97%**	**0.59[0.41,0.83]**
Total events: 370 (Calcium), 456 (Placebo)					
Heterogeneity: Tau²=0.12; Chi²=23.09, df=7(P=0); I²=69.69%					
Test for overall effect: Z=2.99(P=0)					
2.2.2 High-risk women					
Niromanesh 2001	1/15	7/15		2.91%	0.14[0.02,1.02]
L-Jaramillo 1990	0/22	8/34		1.56%	0.09[0.01,1.48]
S-Ramos 1994	4/29	15/34		7.81%	0.31[0.12,0.84]
Villar 1990	0/90	3/88		1.42%	0.14[0.01,2.67]
L-Jaramillo 1997	4/125	21/135		7.33%	0.21[0.07,0.58]
Subtotal (95% CI)	**281**	**306**		**21.03%**	**0.22[0.12,0.42]**
Total events: 9 (Calcium), 54 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.23, df=4(P=0.87); I²=0%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

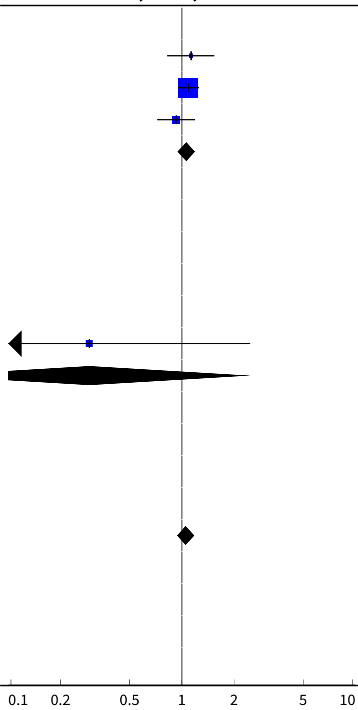
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=4.62(P<0.0001)					
Total (95% CI)	**7851**	**7879**		**100%**	**0.45[0.31,0.65]**
Total events: 379 (Calcium), 510 (Placebo)					
Heterogeneity: Tau²=0.2; Chi²=40.31, df=12(P<0.0001); I²=70.23%					
Test for overall effect: Z=4.29(P<0.0001)					
Test for subgroup differences: Chi²=6.81, df=1 (P=0.01), I²=85.31%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 2.3. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 3 Preterm birth.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Low-risk women					
Villar 1987	0/25	0/27			Not estimable
Purwar 1996	2/97	6/93		2.09%	0.32[0.07,1.54]
Crowther 1999	10/227	23/229		7.89%	0.44[0.21,0.9]
Belizan 1991	33/527	37/542		14.09%	0.92[0.58,1.44]
CPEP 1997	248/2163	229/2173		25.49%	1.09[0.92,1.29]
WHO 2006	398/4038	436/4042		26.99%	0.91[0.8,1.04]
Kumar 2009	19/273	32/251		11.55%	0.55[0.32,0.94]
Subtotal (95% CI)	**7350**	**7357**		**88.09%**	**0.84[0.67,1.05]**
Total events: 710 (Calcium), 763 (Placebo)					
Heterogeneity: Tau²=0.04; Chi²=13.05, df=5(P=0.02); I²=61.68%					
Test for overall effect: Z=1.52(P=0.13)					
2.3.2 High-risk women					
L-Jaramillo 1990	0/22	4/34		0.66%	0.17[0.01,2.99]
S-Ramos 1994	5/29	8/34		4.68%	0.73[0.27,1.99]
Villar 1990	7/94	20/95		6.57%	0.35[0.16,0.8]
L-Jaramillo 1997	0/125	0/135			Not estimable
Subtotal (95% CI)	**270**	**298**		**11.91%**	**0.45[0.24,0.83]**
Total events: 12 (Calcium), 32 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.73, df=2(P=0.42); I²=0%					
Test for overall effect: Z=2.54(P=0.01)					
Total (95% CI)	**7620**	**7655**		**100%**	**0.76[0.6,0.97]**
Total events: 722 (Calcium), 795 (Placebo)					
Heterogeneity: Tau²=0.05; Chi²=20.04, df=8(P=0.01); I²=60.07%					
Test for overall effect: Z=2.23(P=0.03)					
Test for subgroup differences: Chi²=3.48, df=1 (P=0.06), I²=71.27%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

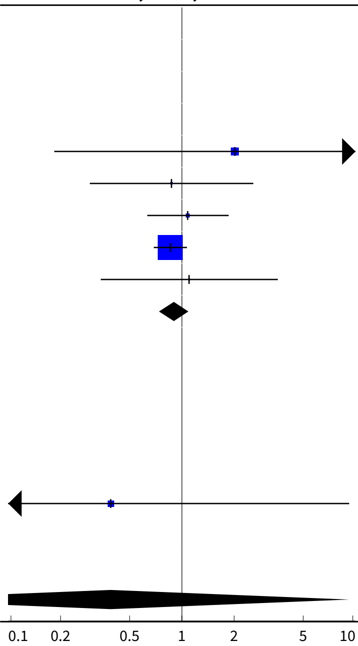
Analysis 2.4. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 4 Admission to neonatal intensive care unit.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Low-risk women					
Belizan 1991	72/544	65/554		12.75%	1.13[0.82,1.54]
CPEP 1997	343/2163	315/2173		62.19%	1.09[0.95,1.26]
WHO 2006	114/3953	123/3956		24.33%	0.93[0.72,1.19]
Subtotal (95% CI)	**6660**	**6683**		**99.27%**	**1.06[0.94,1.19]**
Total events: 529 (Calcium), 503 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.43, df=2(P=0.49); I²=0%					
Test for overall effect: Z=0.96(P=0.34)					
2.4.2 High-risk women					
S-Ramos 1994	1/29	4/34		0.73%	0.29[0.03,2.48]
Subtotal (95% CI)	**29**	**34**		**0.73%**	**0.29[0.03,2.48]**
Total events: 1 (Calcium), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.13(P=0.26)					
Total (95% CI)	**6689**	**6717**		**100%**	**1.05[0.94,1.18]**
Total events: 530 (Calcium), 507 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.83, df=3(P=0.42); I²=0%					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: Chi²=1.38, df=1 (P=0.24), I²=27.75%					

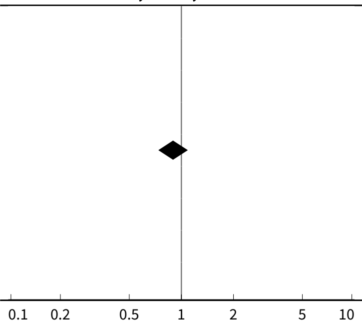


Analysis 2.5. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 5 Stillbirth or death before discharge from hospital.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Low-risk women					
Villar 1987	0/25	0/27			Not estimable
L-Jaramillo 1989	0/49	0/43			Not estimable
Purwar 1996	0/97	0/93			Not estimable
Crowther 1999	2/227	1/229		0.49%	2.02[0.18,22.09]
Belizan 1991	6/558	7/567		3.38%	0.87[0.29,2.58]
CPEP 1997	27/2163	25/2173		12.16%	1.08[0.63,1.86]
WHO 2006	142/4181	166/4197		80.76%	0.86[0.69,1.07]
Kumar 2009	6/273	5/251		2.54%	1.1[0.34,3.57]
Subtotal (95% CI)	**7573**	**7580**		**99.33%**	**0.9[0.74,1.09]**
Total events: 183 (Calcium), 204 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.19, df=4(P=0.88); I²=0%					
Test for overall effect: Z=1.07(P=0.29)					
2.5.2 High-risk women					
S-Ramos 1994	0/29	1/34		0.67%	0.39[0.02,9.2]
Villar 1990	0/94	0/95			Not estimable
L-Jaramillo 1997	0/125	0/135			Not estimable
Subtotal (95% CI)	**248**	**264**		**0.67%**	**0.39[0.02,9.2]**



Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 0 (Calcium), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
Total (95% CI)	**7821**	**7844**		**100%**	**0.9[0.74,1.09]**
Total events: 183 (Calcium), 205 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.46, df=5(P=0.92); I²=0%					
Test for overall effect: Z=1.11(P=0.27)					
Test for subgroup differences: Chi²=0.27, df=1 (P=0.6), I²=0%					



Favours calcium — Favours placebo

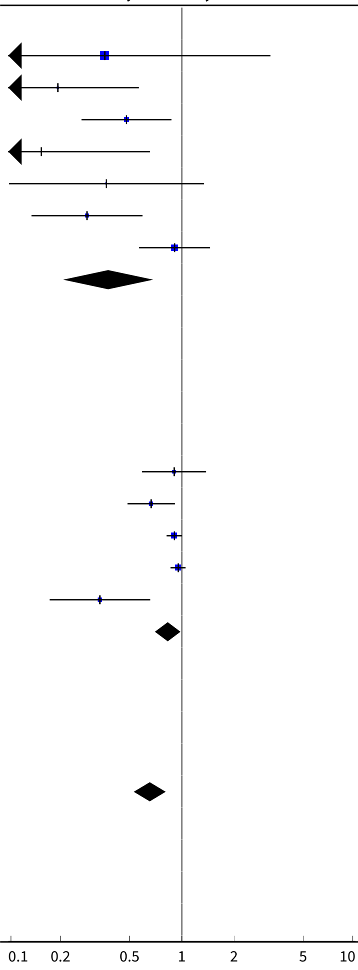
Comparison 3. Routine high-dose calcium supplementation in pregnancy by study sample size

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without proteinuria)	12	15470	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.81]
1.1 Studies with < 400 participants	7	675	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.21, 0.68]
1.2 Studies with =/> 400 participants	5	14795	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
2 Pre-eclampsia	13	15730	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.31, 0.65]
2.1 Studies with < 400 participants	8	935	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.12, 0.36]
2.2 Studies with =/> 400 participants	5	14795	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.97]
3 Preterm birth	11	15275	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
3.1 Studies with < 400 participants	6	810	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.24, 0.76]
3.2 Studies with =/> 400 participants	5	14465	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.07]
4 Admission to neonatal intensive care unit	4	13406	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
4.1 Studies with < 400 participants	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.03, 2.48]
4.2 Studies with =/> 400 participants	3	13343	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Stillbirth or death before discharge from hospital	11	15665	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.09]
5.1 Studies with < 400 participants	6	846	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 9.20]
5.2 Studies with =/> 400 participants	5	14819	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.09]

Analysis 3.1. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 1 High blood pressure (with or without proteinuria).

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Studies with < 400 participants					
Villar 1987	1/25	3/27		0.89%	0.36[0.04,3.24]
L-Jaramillo 1990	3/22	24/34		3.24%	0.19[0.07,0.57]
S-Ramos 1994	9/29	22/34		7.64%	0.48[0.26,0.87]
L-Jaramillo 1989	2/55	12/51		1.93%	0.15[0.04,0.66]
Villar 1990	3/90	8/88		2.36%	0.37[0.1,1.34]
Purwar 1996	8/97	27/93		5.81%	0.28[0.14,0.59]
Niromanesh 2001	10/15	11/15		9.92%	0.91[0.57,1.45]
Subtotal (95% CI)	**333**	**342**		**31.79%**	**0.38[0.21,0.68]**
Total events: 36 (Calcium), 107 (Placebo)					
Heterogeneity: Tau²=0.38; Chi²=18.26, df=6(P=0.01); I²=67.15%					
Test for overall effect: Z=3.2(P=0)					
3.1.2 Studies with =/> 400 participants					
Crowther 1999	34/227	38/229		10.9%	0.9[0.59,1.38]
Belizan 1991	57/579	87/588		13.61%	0.67[0.49,0.91]
CPEP 1997	509/2163	565/2173		18.53%	0.91[0.82,1]
WHO 2006	613/4151	645/4161		18.56%	0.95[0.86,1.05]
Kumar 2009	11/273	30/251		6.61%	0.34[0.17,0.66]
Subtotal (95% CI)	**7393**	**7402**		**68.21%**	**0.83[0.7,0.98]**
Total events: 1224 (Calcium), 1365 (Placebo)					
Heterogeneity: Tau²=0.02; Chi²=13.05, df=4(P=0.01); I²=69.34%					
Test for overall effect: Z=2.17(P=0.03)					
Total (95% CI)	**7726**	**7744**		**100%**	**0.65[0.53,0.81]**
Total events: 1260 (Calcium), 1472 (Placebo)					
Heterogeneity: Tau²=0.06; Chi²=42.4, df=11(P<0.0001); I²=74.06%					
Test for overall effect: Z=3.95(P<0.0001)					
Test for subgroup differences: Chi²=6.2, df=1 (P=0.01), I²=83.86%					



Analysis 3.2. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 2 Pre-eclampsia.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Studies with < 400 participants					
Niromanesh 2001	1/15	7/15		2.91%	0.14[0.02,1.02]
L-Jaramillo 1990	0/22	8/34		1.56%	0.09[0.01,1.48]
Villar 1987	1/25	3/27		2.41%	0.36[0.04,3.24]
S-Ramos 1994	4/29	15/34		7.81%	0.31[0.12,0.84]
L-Jaramillo 1989	2/55	12/51		4.72%	0.15[0.04,0.66]
Villar 1990	0/90	3/88		1.42%	0.14[0.01,2.67]
Purwar 1996	2/97	11/93		4.57%	0.17[0.04,0.77]
L-Jaramillo 1997	4/125	21/135		7.33%	0.21[0.07,0.58]
Subtotal (95% CI)	**458**	**477**		**32.74%**	**0.21[0.12,0.36]**
Total events: 14 (Calcium), 80 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.72, df=7(P=0.97); I²=0%					
Test for overall effect: Z=5.78(P<0.0001)					
3.2.2 Studies with =/> 400 participants					
Crowther 1999	10/227	23/229		10.6%	0.44[0.21,0.9]
Belizan 1991	15/579	23/588		11.58%	0.66[0.35,1.26]
CPEP 1997	158/2163	168/2173		16.91%	0.94[0.77,1.16]
WHO 2006	171/4151	186/4161		16.96%	0.92[0.75,1.13]
Kumar 2009	11/273	30/251		11.21%	0.34[0.17,0.66]
Subtotal (95% CI)	**7393**	**7402**		**67.26%**	**0.71[0.52,0.97]**
Total events: 365 (Calcium), 430 (Placebo)					
Heterogeneity: Tau²=0.07; Chi²=12.77, df=4(P=0.01); I²=68.67%					
Test for overall effect: Z=2.18(P=0.03)					
Total (95% CI)	**7851**	**7879**		**100%**	**0.45[0.31,0.65]**
Total events: 379 (Calcium), 510 (Placebo)					
Heterogeneity: Tau²=0.2; Chi²=40.31, df=12(P<0.0001); I²=70.23%					
Test for overall effect: Z=4.29(P<0.0001)					
Test for subgroup differences: Chi²=15.2, df=1 (P<0.0001), I²=93.42%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 3.3. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 3 Preterm birth.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Studies with < 400 participants					
Villar 1987	0/25	0/27			Not estimable
L-Jaramillo 1990	0/22	4/34		0.66%	0.17[0.01,2.99]
S-Ramos 1994	5/29	8/34		4.68%	0.73[0.27,1.99]
Purwar 1996	2/97	6/93		2.09%	0.32[0.07,1.54]
Villar 1990	7/94	20/95		6.57%	0.35[0.16,0.8]
L-Jaramillo 1997	0/125	0/135			Not estimable
Subtotal (95% CI)	**392**	**418**		**14%**	**0.43[0.24,0.76]**
Total events: 14 (Calcium), 38 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.89, df=3(P=0.6); I²=0%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours placebo	

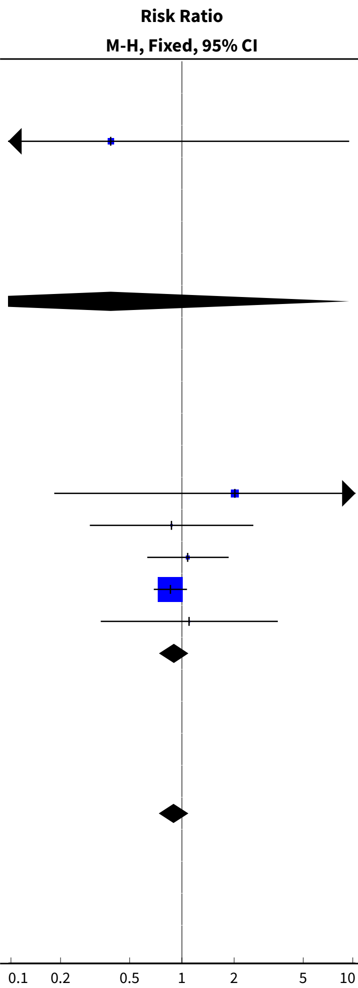
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.88(P=0)					
3.3.2 Studies with =/> 400 participants					
Crowther 1999	10/227	23/229		7.89%	0.44[0.21,0.9]
Belizan 1991	33/527	37/542		14.09%	0.92[0.58,1.44]
CPEP 1997	248/2163	229/2173		25.49%	1.09[0.92,1.29]
WHO 2006	398/4038	436/4042		26.99%	0.91[0.8,1.04]
Kumar 2009	19/273	32/251		11.55%	0.55[0.32,0.94]
Subtotal (95% CI)	**7228**	**7237**		**86%**	**0.86[0.69,1.07]**
Total events: 708 (Calcium), 757 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=11.25, df=4(P=0.02); I^2=64.44%					
Test for overall effect: Z=1.33(P=0.18)					
Total (95% CI)	**7620**	**7655**		**100%**	**0.76[0.6,0.97]**
Total events: 722 (Calcium), 795 (Placebo)					
Heterogeneity: Tau^2=0.05; Chi^2=20.04, df=8(P=0.01); I^2=60.07%					
Test for overall effect: Z=2.23(P=0.03)					
Test for subgroup differences: Chi^2=4.9, df=1 (P=0.03), I^2=79.6%					
	Favours calcium		0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 3.4. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 4 Admission to neonatal intensive care unit.

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Studies with < 400 participants					
S-Ramos 1994	1/29	4/34		0.73%	0.29[0.03,2.48]
Subtotal (95% CI)	**29**	**34**		**0.73%**	**0.29[0.03,2.48]**
Total events: 1 (Calcium), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.13(P=0.26)					
3.4.2 Studies with =/> 400 participants					
Belizan 1991	72/544	65/554		12.75%	1.13[0.82,1.54]
CPEP 1997	343/2163	315/2173		62.19%	1.09[0.95,1.26]
WHO 2006	114/3953	123/3956		24.33%	0.93[0.72,1.19]
Subtotal (95% CI)	**6660**	**6683**		**99.27%**	**1.06[0.94,1.19]**
Total events: 529 (Calcium), 503 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.43, df=2(P=0.49); I^2=0%					
Test for overall effect: Z=0.96(P=0.34)					
Total (95% CI)	**6689**	**6717**		**100%**	**1.05[0.94,1.18]**
Total events: 530 (Calcium), 507 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.83, df=3(P=0.42); I^2=0%					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: Chi^2=1.38, df=1 (P=0.24), I^2=27.75%					
	Favours calcium		0.1 0.2 0.5 1 2 5 10	Favours placebo	

Analysis 3.5. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 5 Stillbirth or death before discharge from hospital.

Study or subgroup	Calcium n/N	Placebo n/N	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Studies with < 400 participants				
Villar 1987	0/25	0/27		Not estimable
S-Ramos 1994	0/29	1/34	0.67%	0.39[0.02,9.2]
L-Jaramillo 1989	0/49	0/43		Not estimable
Villar 1990	0/94	0/95		Not estimable
Purwar 1996	0/97	0/93		Not estimable
L-Jaramillo 1997	0/125	0/135		Not estimable
Subtotal (95% CI)	**419**	**427**	**0.67%**	**0.39[0.02,9.2]**
Total events: 0 (Calcium), 1 (Placebo)				
Heterogeneity: Not applicable				
Test for overall effect: Z=0.59(P=0.56)				
3.5.2 Studies with =/> 400 participants				
Crowther 1999	2/227	1/229	0.49%	2.02[0.18,22.09]
Belizan 1991	6/558	7/567	3.38%	0.87[0.29,2.58]
CPEP 1997	27/2163	25/2173	12.16%	1.08[0.63,1.86]
WHO 2006	142/4181	166/4197	80.76%	0.86[0.69,1.07]
Kumar 2009	6/273	5/251	2.54%	1.1[0.34,3.57]
Subtotal (95% CI)	**7402**	**7417**	**99.33%**	**0.9[0.74,1.09]**
Total events: 183 (Calcium), 204 (Placebo)				
Heterogeneity: Tau²=0; Chi²=1.19, df=4(P=0.88); I²=0%				
Test for overall effect: Z=1.07(P=0.29)				
Total (95% CI)	**7821**	**7844**	**100%**	**0.9[0.74,1.09]**
Total events: 183 (Calcium), 205 (Placebo)				
Heterogeneity: Tau²=0; Chi²=1.46, df=5(P=0.92); I²=0%				
Test for overall effect: Z=1.11(P=0.27)				
Test for subgroup differences: Chi²=0.27, df=1 (P=0.6), I²=0%				



Favours calcium   Favours placebo

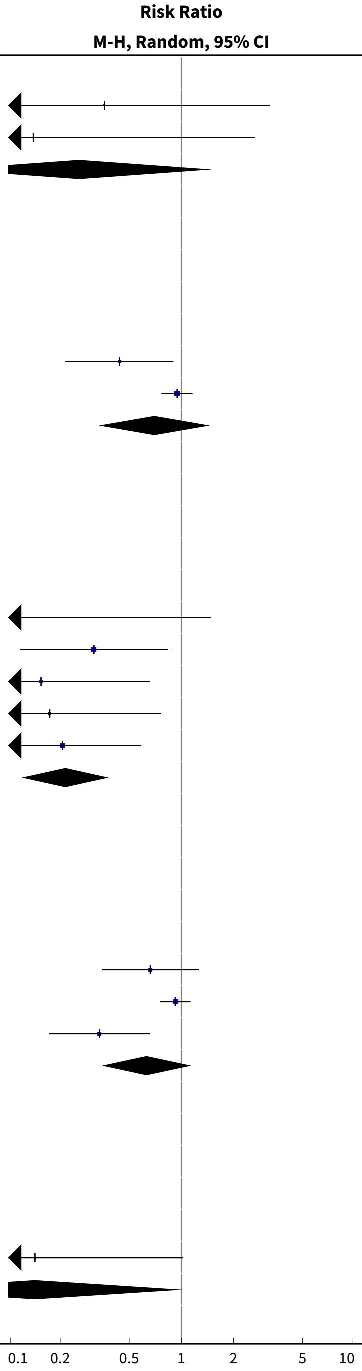
Comparison 4. Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium and study sample size (not prespecified)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pre-eclampsia	13	15730	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.31, 0.65]
1.1 Adequate calcium/small study	2	230	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.04, 1.50]
1.2 Adequate calcium/large study	2	4792	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.33, 1.46]
1.3 Low calcium/small study	5	675	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.12, 0.38]
1.4 Low calcium/large study	3	10003	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.35, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Dietary calcium not specified	1	30	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.02]

Analysis 4.1. Comparison 4 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium and study sample size (not prespecified), Outcome 1 Pre-eclampsia.

Study or subgroup	Calcium n/N	Placebo n/N	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Adequate calcium/small study				
Villar 1987	1/25	3/27	2.41%	0.36[0.04,3.24]
Villar 1990	0/90	3/88	1.42%	0.14[0.01,2.67]
Subtotal (95% CI)	**115**	**115**	**3.84%**	**0.26[0.04,1.5]**
Total events: 1 (Calcium), 6 (Placebo)				
Heterogeneity: Tau²=0; Chi²=0.26, df=1(P=0.61); I²=0%				
Test for overall effect: Z=1.51(P=0.13)				
4.1.2 Adequate calcium/large study				
Crowther 1999	10/227	23/229	10.6%	0.44[0.21,0.9]
CPEP 1997	158/2163	168/2173	16.91%	0.94[0.77,1.16]
Subtotal (95% CI)	**2390**	**2402**	**27.51%**	**0.7[0.33,1.46]**
Total events: 168 (Calcium), 191 (Placebo)				
Heterogeneity: Tau²=0.22; Chi²=4.04, df=1(P=0.04); I²=75.22%				
Test for overall effect: Z=0.96(P=0.34)				
4.1.3 Low calcium/small study				
L-Jaramillo 1990	0/22	8/34	1.56%	0.09[0.01,1.48]
S-Ramos 1994	4/29	15/34	7.81%	0.31[0.12,0.84]
L-Jaramillo 1989	2/55	12/51	4.72%	0.15[0.04,0.66]
Purwar 1996	2/97	11/93	4.57%	0.17[0.04,0.77]
L-Jaramillo 1997	4/125	21/135	7.33%	0.21[0.07,0.58]
Subtotal (95% CI)	**328**	**347**	**26%**	**0.21[0.12,0.38]**
Total events: 12 (Calcium), 67 (Placebo)				
Heterogeneity: Tau²=0; Chi²=1.26, df=4(P=0.87); I²=0%				
Test for overall effect: Z=5.25(P<0.0001)				
4.1.4 Low calcium/large study				
Belizan 1991	15/579	23/588	11.58%	0.66[0.35,1.26]
WHO 2006	171/4151	186/4161	16.96%	0.92[0.75,1.13]
Kumar 2009	11/273	30/251	11.21%	0.34[0.17,0.66]
Subtotal (95% CI)	**5003**	**5000**	**39.75%**	**0.63[0.35,1.14]**
Total events: 197 (Calcium), 239 (Placebo)				
Heterogeneity: Tau²=0.21; Chi²=8.47, df=2(P=0.01); I²=76.39%				
Test for overall effect: Z=1.54(P=0.12)				
4.1.5 Dietary calcium not specified				
Niromanesh 2001	1/15	7/15	2.91%	0.14[0.02,1.02]
Subtotal (95% CI)	**15**	**15**	**2.91%**	**0.14[0.02,1.02]**
Total events: 1 (Calcium), 7 (Placebo)				



Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.94(P=0.05)					
Total (95% CI)	**7851**	**7879**		**100%**	**0.45[0.31,0.65]**
Total events: 379 (Calcium), 510 (Placebo)					
Heterogeneity: Tau²=0.2; Chi²=40.31, df=12(P<0.0001); I²=70.23%					
Test for overall effect: Z=4.29(P<0.0001)					
Test for subgroup differences: Chi²=10.28, df=1 (P=0.04), I²=61.11%					

Favours calcium 0.1 0.2 0.5 1 2 5 10 Favours placebo

Comparison 5. Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified)

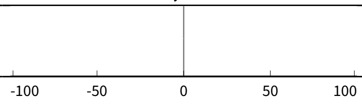
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine artery RI at 32 weeks	1	372	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
2 Umbilical artery RI at 32 weeks	1	373	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
3 Low platelet count at 35 weeks	1	667	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.18]
4 High serum uric acid at 35 weeks	1	664	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.64, 1.57]
5 High urine protein/creatinine ratio at 35 weeks	1	637	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.76, 1.34]
6 Ultrasound estimate of fetal growth at 32 weeks: femur length (cm)*	1	377	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.04, 0.04]
7 Ultrasound estimate of fetal growth at 32 weeks: biparietal diameter (cm)*	1	377	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.06, 0.06]
8 Ultrasound estimate of fetal growth at 32 weeks: abdominal circumference (cm)*	1	377	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.26, 0.26]

Analysis 5.1. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 1 Uterine artery RI at 32 weeks.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
WHO 2006	184	0.5 (0.1)	188	0.5 (0.1)		100%	-0.01[-0.02,0.01]
Total ***	**184**		**188**			**100%**	**-0.01[-0.02,0.01]**

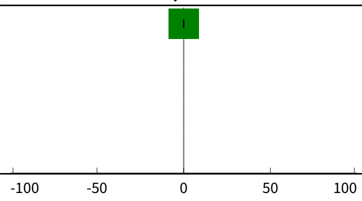
Favours experimental -100 -50 0 50 100 Favours control

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=0.79(P=0.43)							



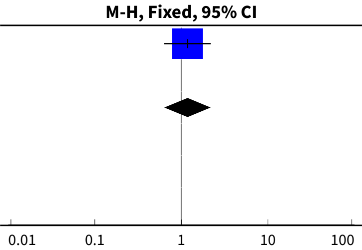
Analysis 5.2. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 2 Umbilical artery RI at 32 weeks.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
WHO 2006	186	0.7 (0.1)	187	0.7 (0.1)		100%	-0.01[-0.02,0.01]
Total ***	**186**		**187**			**100%**	**-0.01[-0.02,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.79(P=0.43)							



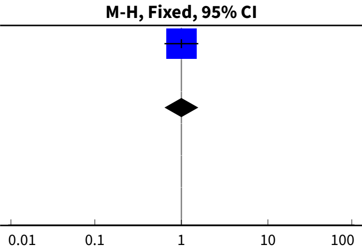
Analysis 5.3. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 3 Low platelet count at 35 weeks.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHO 2006	20/324	18/343		100%	1.18[0.63,2.18]
Total (95% CI)	**324**	**343**		**100%**	**1.18[0.63,2.18]**
Total events: 20 (Experimental), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					



Analysis 5.4. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 4 High serum uric acid at 35 weeks.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHO 2006	33/322	35/342		100%	1[0.64,1.57]
Total (95% CI)	**322**	**342**		**100%**	**1[0.64,1.57]**
Total events: 33 (Experimental), 35 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=1)					



Analysis 5.5. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 5 High urine protein/creatinine ratio at 35 weeks.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
WHO 2006	71/308	75/329		100%	1.01[0.76,1.34]
Total (95% CI)	**308**	**329**		**100%**	**1.01[0.76,1.34]**
Total events: 71 (Experimental), 75 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.94)					
	Favours experimental		0.01 0.1 1 10 100	Favours control	

Analysis 5.6. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 6 Ultrasound estimate of fetal growth at 32 weeks: femur length (cm)*.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
WHO 2006	186	6.2 (0.2)	191	6.2 (0.2)		100%	0[-0.04,0.04]
Total ***	**186**		**191**			**100%**	**0[-0.04,0.04]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
			Favours experimental		-100 -50 0 50 100	Favours control	

Analysis 5.7. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 7 Ultrasound estimate of fetal growth at 32 weeks: biparietal diameter (cm)*.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
WHO 2006	186	8 (0.3)	191	8 (0.3)		100%	0[-0.06,0.06]
Total ***	**186**		**191**			**100%**	**0[-0.06,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
			Favours experimental		-100 -50 0 50 100	Favours control	

Analysis 5.8. Comparison 5 Routine high-dose calcium supplementation in pregnancy by other outcomes (not prespecified), Outcome 8 Ultrasound estimate of fetal growth at 32 weeks: abdominal circumference (cm)*.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
WHO 2006	186	27.9 (1.3)	191	27.9 (1.3)		100%	0[-0.26,0.26]
Total ***	**186**		**191**			**100%**	**0[-0.26,0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
			Favours experimental		-100 -50 0 50 100	Favours control	

Comparison 6. Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment

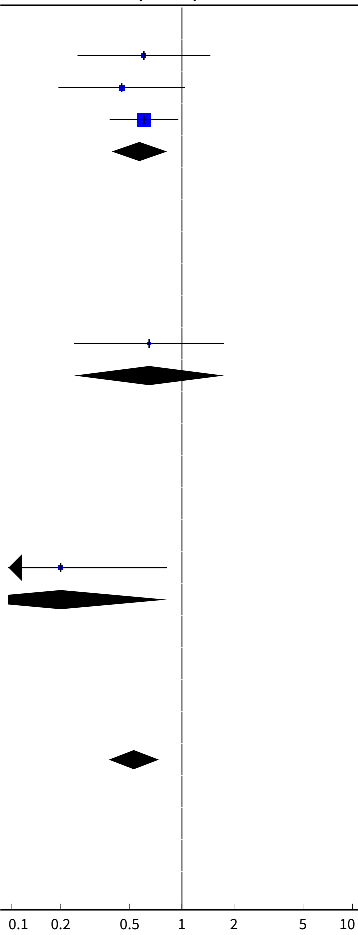
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without pre-eclampsia)	5	665	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.38, 0.74]
1.1 Calcium supplementation alone	3	558	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.39, 0.82]
1.2 Calcium plus vitamin D	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.75]
1.3 Calcium plus linoleic acid	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.82]
2 Pre-eclampsia	9	2234	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.28, 0.52]
2.1 Calcium supplementation alone	4	980	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.57]
2.2 Calcium plus vitamin D	2	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.31, 0.78]
2.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.09, 0.60]
2.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.01]
3 Preterm birth	6	1290	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.34, 2.03]
3.1 Calcium supplementation alone	1	422	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.75]
3.2 Calcium plus vitamin D	3	760	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.03, 2.45]
3.3 Calcium plus linoleic acid	1	48	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.15]
3.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.23]
4 Admission to neonatal intensive care unit	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.20, 0.99]
4.1 Calcium supplementation alone	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.20, 0.99]
4.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Calcium plus linoleic acid	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Stillbirth or death before discharge	5	1025	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.14, 1.67]
5.1 Calcium supplementation alone	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.29]
5.2 Calcium plus vitamin D	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.08, 4.41]
5.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.39]
6 Placental abruption	3	160	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 6.90]
6.1 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Calcium plus vitamin D	2	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 6.90]
7 Caesarean section	4	521	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.15]
7.1 Calcium supplementation alone	2	387	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.40, 2.22]
7.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.35, 0.87]
8 Severe pre-eclampsia	4	246	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.14, 1.15]
8.1 Calcium supplementation alone	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Calcium plus vitamin D	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.08, 4.39]
8.3 Calcium plus linoleic acid	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.56]
8.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.04, 3.23]
9 Eclampsia	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.06]
9.1 Calcium supplementation alone	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.06]
9.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Calcium plus linoleic acid	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Miscarriage	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.04]
10.1 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 1.04]
11 Low birthweight (birthweight < 2500 g)	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.88]
11.1 Calcium supplementation alone	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Neonate small-for-gestational age	4	854	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.21]
12.1 Calcium supplementation alone	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Calcium plus vitamin D	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.38]
12.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.32]
12.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 16.31]

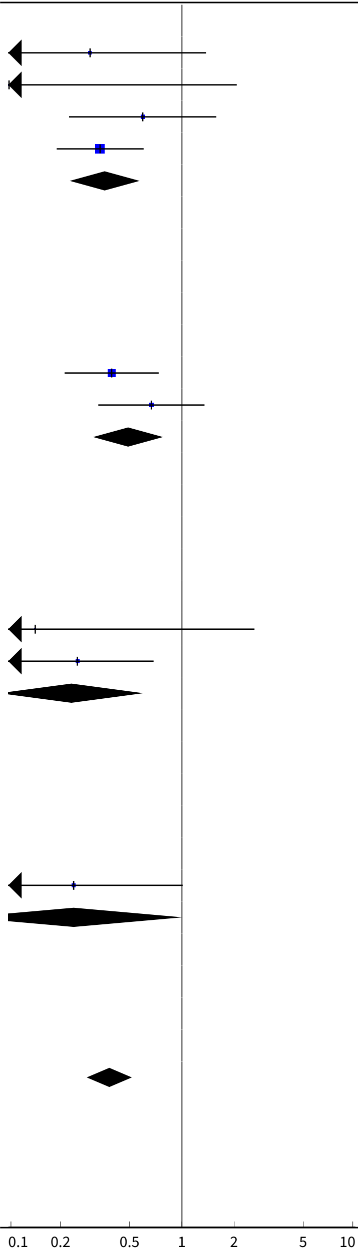
Analysis 6.1. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 1 High blood pressure (with or without pre-eclampsia).

Study or subgroup	Calcium n/N	Control n/N	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Calcium supplementation alone				
Bassaw 1998	7/84	12/87	15.54%	0.6[0.25,1.46]
Cong 1995	9/112	10/56	17.58%	0.45[0.19,1.04]
Rogers 1999	29/144	25/75	43.34%	0.6[0.38,0.95]
Subtotal (95% CI)	**340**	**218**	**76.45%**	**0.57[0.39,0.82]**
Total events: 45 (Calcium), 47 (Control)				
Heterogeneity: Tau²=0; Chi²=0.38, df=2(P=0.83); I²=0%				
Test for overall effect: Z=3.01(P=0)				
6.1.2 Calcium plus vitamin D				
Li 2000	5/29	8/30	10.37%	0.65[0.24,1.75]
Subtotal (95% CI)	**29**	**30**	**10.37%**	**0.65[0.24,1.75]**
Total events: 5 (Calcium), 8 (Control)				
Heterogeneity: Not applicable				
Test for overall effect: Z=0.86(P=0.39)				
6.1.3 Calcium plus linoleic acid				
Herrera 2006	2/24	10/24	13.18%	0.2[0.05,0.82]
Subtotal (95% CI)	**24**	**24**	**13.18%**	**0.2[0.05,0.82]**
Total events: 2 (Calcium), 10 (Control)				
Heterogeneity: Not applicable				
Test for overall effect: Z=2.24(P=0.03)				
Total (95% CI)	**393**	**272**	**100%**	**0.53[0.38,0.74]**
Total events: 52 (Calcium), 65 (Control)				
Heterogeneity: Tau²=0; Chi²=2.55, df=4(P=0.64); I²=0%				
Test for overall effect: Z=3.76(P=0)				
Test for subgroup differences: Chi²=2.11, df=1 (P=0.35), I²=5.22%				



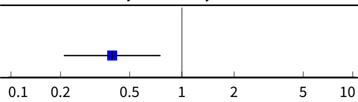
Analysis 6.2. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 2 Pre-eclampsia.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 Calcium supplementation alone					
Bassaw 1998	2/84	7/87		4.92%	0.3[0.06,1.38]
Cong 1995	0/112	2/56		2.38%	0.1[0,2.07]
Rogers 1999	8/144	7/75		6.58%	0.6[0.22,1.58]
Almirante 1998	14/212	41/210		29.47%	0.34[0.19,0.6]
Subtotal (95% CI)	**552**	**428**		**43.35%**	**0.36[0.23,0.57]**
Total events: 24 (Calcium), 57 (Control)					
Heterogeneity: Tau²=0; Chi²=1.81, df=3(P=0.61); I²=0%					
Test for overall effect: Z=4.34(P<0.0001)					
6.2.2 Calcium plus vitamin D					
Taherian 2002	13/330	33/330		23.61%	0.39[0.21,0.73]
Marya 1987	12/200	18/200		12.88%	0.67[0.33,1.35]
Subtotal (95% CI)	**530**	**530**		**36.48%**	**0.49[0.31,0.78]**
Total events: 25 (Calcium), 51 (Control)					
Heterogeneity: Tau²=0; Chi²=1.21, df=1(P=0.27); I²=17.08%					
Test for overall effect: Z=3.02(P=0)					
6.2.3 Calcium plus linoleic acid					
Herrera 2006	0/24	3/24		2.5%	0.14[0.01,2.62]
Herrera 1998	4/43	16/43		11.44%	0.25[0.09,0.69]
Subtotal (95% CI)	**67**	**67**		**13.95%**	**0.23[0.09,0.6]**
Total events: 4 (Calcium), 19 (Control)					
Heterogeneity: Tau²=0; Chi²=0.13, df=1(P=0.72); I²=0%					
Test for overall effect: Z=3.01(P=0)					
6.2.4 Calcium plus antioxidants					
Rumiris 2006	2/29	9/31		6.22%	0.24[0.06,1.01]
Subtotal (95% CI)	**29**	**31**		**6.22%**	**0.24[0.06,1.01]**
Total events: 2 (Calcium), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					
Total (95% CI)	**1178**	**1056**		**100%**	**0.38[0.28,0.52]**
Total events: 55 (Calcium), 136 (Control)					
Heterogeneity: Tau²=0; Chi²=5.76, df=8(P=0.67); I²=0%					
Test for overall effect: Z=6.28(P<0.0001)					
Test for subgroup differences: Chi²=2.66, df=1 (P=0.45), I²=0%					



Analysis 6.3. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 3 Preterm birth.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Calcium supplementation alone					
Almirante 1998	12/212	30/210		31.1%	0.4[0.21,0.75]



Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**212**	**210**		**31.1%**	**0.4[0.21,0.75]**
Total events: 12 (Calcium), 30 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.83(P=0)					
6.3.2 Calcium plus vitamin D					
Asemi 2012	1/27	0/27		6.55%	3[0.13,70.53]
Asemi 2016	1/23	0/23		6.57%	3[0.13,70.02]
Taherian 2002	45/330	29/330		33.99%	1.55[1,2.41]
Subtotal (95% CI)	**380**	**380**		**47.12%**	**1.59[1.03,2.45]**
Total events: 47 (Calcium), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=2.1(P=0.04)					
6.3.3 Calcium plus linoleic acid					
Herrera 2006	1/24	2/24		10.46%	0.5[0.05,5.15]
Subtotal (95% CI)	**24**	**24**		**10.46%**	**0.5[0.05,5.15]**
Total events: 1 (Calcium), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					
6.3.4 Calcium plus antioxidants					
Rumiris 2006	1/29	3/31		11.32%	0.36[0.04,3.23]
Subtotal (95% CI)	**29**	**31**		**11.32%**	**0.36[0.04,3.23]**
Total events: 1 (Calcium), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.92(P=0.36)					
Total (95% CI)	**645**	**645**		**100%**	**0.83[0.34,2.03]**
Total events: 61 (Calcium), 64 (Control)					
Heterogeneity: Tau^2=0.56; Chi^2=13.95, df=5(P=0.02); I^2=64.16%					
Test for overall effect: Z=0.4(P=0.69)					
Test for subgroup differences: Chi^2=13.59, df=1 (P=0), I^2=77.93%					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours control	

Analysis 6.4. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 4 Admission to neonatal intensive care unit.

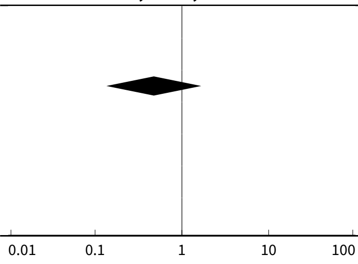
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.1 Calcium supplementation alone					
Almirante 1998	8/212	18/210		100%	0.44[0.2,0.99]
Subtotal (95% CI)	**212**	**210**		**100%**	**0.44[0.2,0.99]**
Total events: 8 (Calcium), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
6.4.2 Calcium plus vitamin D					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours control	

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.4.3 Calcium plus linoleic acid					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**212**	**210**		**100%**	**0.44[0.2,0.99]**
Total events: 8 (Calcium), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
Test for subgroup differences: Not applicable					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours control	

Analysis 6.5. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 5 Stillbirth or death before discharge.

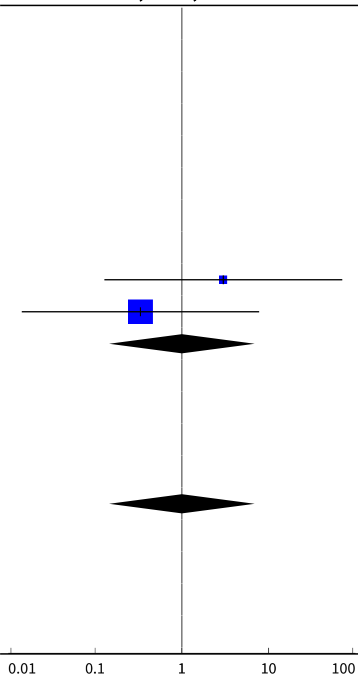
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.5.1 Calcium supplementation alone					
Bassaw 1998	1/84	1/87		13.22%	1.04[0.07,16.29]
Subtotal (95% CI)	**84**	**87**		**13.22%**	**1.04[0.07,16.29]**
Total events: 1 (Calcium), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.98)					
6.5.2 Calcium plus vitamin D					
Taherian 2002	0/330	2/330		33.63%	0.2[0.01,4.15]
Subtotal (95% CI)	**330**	**330**		**33.63%**	**0.2[0.01,4.15]**
Total events: 0 (Calcium), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
6.5.3 Calcium plus linoleic acid					
Herrera 1998	0/43	1/43		20.18%	0.33[0.01,7.96]
Herrera 2006	1/24	1/24		13.45%	1[0.07,15.08]
Subtotal (95% CI)	**67**	**67**		**33.63%**	**0.6[0.08,4.41]**
Total events: 1 (Calcium), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					
6.5.4 Calcium plus antioxidants					
Rumiris 2006	0/29	1/31		19.53%	0.36[0.02,8.39]
Subtotal (95% CI)	**29**	**31**		**19.53%**	**0.36[0.02,8.39]**
Total events: 0 (Calcium), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
		Favours calcium	0.01 0.1 1 10 100	Favours control	

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.64(P=0.52)					
Total (95% CI)	**510**	**515**		**100%**	**0.48[0.14,1.67]**
Total events: 2 (Calcium), 6 (Control)					
Heterogeneity: Tau²=0; Chi²=0.99, df=4(P=0.91); I²=0%					
Test for overall effect: Z=1.16(P=0.25)					
Test for subgroup differences: Chi²=0.7, df=1 (P=0.87), I²=0%					



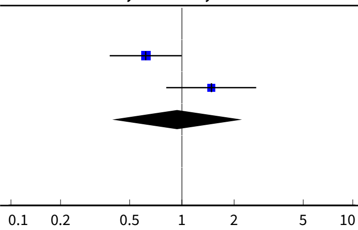
Analysis 6.6. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 6 Placental abruption.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.6.1 Calcium plus antioxidants					
Rumiris 2006	0/29	0/31			Not estimable
Subtotal (95% CI)	**29**	**31**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.6.2 Calcium plus vitamin D					
Asemi 2012	1/27	0/27		25%	3[0.13,70.53]
Asemi 2016	0/23	1/23		75%	0.33[0.01,7.78]
Subtotal (95% CI)	**50**	**50**		**100%**	**1[0.14,6.9]**
Total events: 1 (Calcium), 1 (Control)					
Heterogeneity: Tau²=0; Chi²=0.93, df=1(P=0.33); I²=0%					
Test for overall effect: Not applicable					
Total (95% CI)	**79**	**81**		**100%**	**1[0.14,6.9]**
Total events: 1 (Calcium), 1 (Control)					
Heterogeneity: Tau²=0; Chi²=0.93, df=1(P=0.33); I²=0%					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					



Analysis 6.7. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 7 Caesarean section.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.7.1 Calcium supplementation alone					
Cong 1995	26/112	21/56		29.07%	0.62[0.38,1]
Rogers 1999	34/144	12/75		24.81%	1.48[0.81,2.68]
Subtotal (95% CI)	**256**	**131**		**53.88%**	**0.94[0.4,2.22]**
Total events: 60 (Calcium), 33 (Control)					
Heterogeneity: Tau²=0.31; Chi²=5.09, df=1(P=0.02); I²=80.36%					



Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.15(P=0.88)					
6.7.2 Calcium plus vitamin D					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.7.3 Calcium plus linoleic acid					
Herrera 1998	10/43	19/43		23.39%	0.53[0.28,1]
Herrera 2006	8/24	14/24		22.73%	0.57[0.3,1.1]
Subtotal (95% CI)	**67**	**67**		**46.12%**	**0.55[0.35,0.87]**
Total events: 18 (Calcium), 33 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.03$, df=1(P=0.86); $I^2=0\%$					
Test for overall effect: Z=2.57(P=0.01)					
Total (95% CI)	**323**	**198**		**100%**	**0.73[0.46,1.15]**
Total events: 78 (Calcium), 66 (Control)					
Heterogeneity: $Tau^2=0.13$; $Chi^2=7.48$, df=3(P=0.06); $I^2=59.92\%$					
Test for overall effect: Z=1.35(P=0.18)					
Test for subgroup differences: $Chi^2=1.17$, df=1 (P=0.28), $I^2=14.54\%$					
		Favours calcium	0.1 0.2 0.5 1 2 5 10	Favours control	

Analysis 6.8. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 8 Severe pre-eclampsia.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.1 Calcium supplementation alone					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.8.2 Calcium plus vitamin D					
Asemi 2016	0/23	1/23		13.16%	0.33[0.01,7.78]
Asemi 2012	1/27	1/27		8.77%	1[0.07,15.18]
Subtotal (95% CI)	**50**	**50**		**21.93%**	**0.6[0.08,4.39]**
Total events: 1 (Calcium), 2 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.27$, df=1(P=0.6); $I^2=0\%$					
Test for overall effect: Z=0.5(P=0.61)					
6.8.3 Calcium plus linoleic acid					
Herrera 1998	2/43	6/43		52.63%	0.33[0.07,1.56]
Subtotal (95% CI)	**43**	**43**		**52.63%**	**0.33[0.07,1.56]**
Total events: 2 (Calcium), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.4(P=0.16)					
		Favours calcium	0.01 0.1 1 10 100	Favours control	

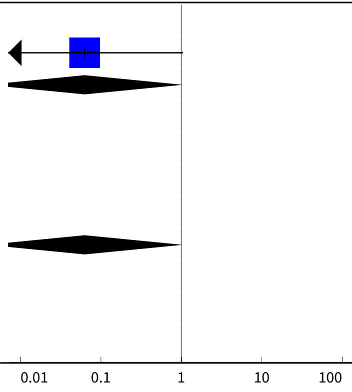
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.4 Calcium plus antioxidants					
Rumiris 2006	1/29	3/31		25.44%	0.36[0.04,3.23]
Subtotal (95% CI)	**29**	**31**		**25.44%**	**0.36[0.04,3.23]**
Total events: 1 (Calcium), 3 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.92(P=0.36)					
Total (95% CI)	**122**	**124**		**100%**	**0.4[0.14,1.15]**
Total events: 4 (Calcium), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=0.51, df=3(P=0.92); I²=0%					
Test for overall effect: Z=1.71(P=0.09)					
Test for subgroup differences: Chi²=0.22, df=1 (P=0.89), I²=0%					
		Favours calcium	0.01 0.1 1 10 100	Favours control	

Analysis 6.9. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 9 Eclampsia.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.9.1 Calcium supplementation alone					
Cong 1995	0/112	1/56		100%	0.17[0.01,4.06]
Subtotal (95% CI)	**112**	**56**		**100%**	**0.17[0.01,4.06]**
Total events: 0 (Calcium), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.1(P=0.27)					
6.9.2 Calcium plus vitamin D					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.9.3 Calcium plus linoleic acid					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**112**	**56**		**100%**	**0.17[0.01,4.06]**
Total events: 0 (Calcium), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.1(P=0.27)					
Test for subgroup differences: Not applicable					
		Favours calcium	0.01 0.1 1 10 100	Favours control	

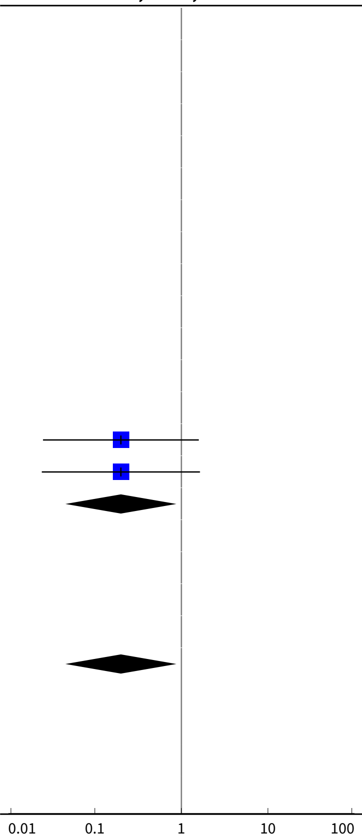
Analysis 6.10. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 10 Miscarriage.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.10.1 Calcium plus antioxidants					
Rumiris 2006	0/29	8/31		100%	0.06[0,1.04]
Subtotal (95% CI)	**29**	**31**		**100%**	**0.06[0,1.04]**
Total events: 0 (Calcium), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					
Total (95% CI)	**29**	**31**		**100%**	**0.06[0,1.04]**
Total events: 0 (Calcium), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					



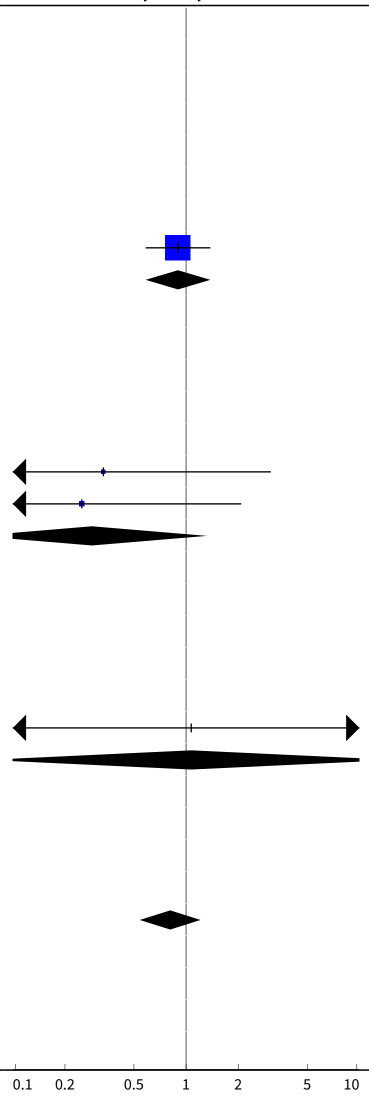
Analysis 6.11. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 11 Low birthweight (birthweight < 2500 g).

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.11.1 Calcium supplementation alone					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.11.2 Calcium plus vitamin D					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.11.3 Calcium plus linoleic acid					
Herrera 2006	1/24	5/24		50%	0.2[0.03,1.59]
Herrera 1998	1/43	5/43		50%	0.2[0.02,1.64]
Subtotal (95% CI)	**67**	**67**		**100%**	**0.2[0.05,0.88]**
Total events: 2 (Calcium), 10 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%					
Test for overall effect: Z=2.14(P=0.03)					
Total (95% CI)	**67**	**67**		**100%**	**0.2[0.05,0.88]**
Total events: 2 (Calcium), 10 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%					
Test for overall effect: Z=2.14(P=0.03)					
Test for subgroup differences: Chi²=0, df=1 (P<0.0001), I²=100%					



Analysis 6.12. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements vs placebo or no treatment, Outcome 12 Neonate small-for-gestational age.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.12.1 Calcium supplementation alone					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.12.2 Calcium plus vitamin D					
Taherian 2002	35/330	39/330		83.04%	0.9[0.58,1.38]
Subtotal (95% CI)	**330**	**330**		**83.04%**	**0.9[0.58,1.38]**
Total events: 35 (Calcium), 39 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
6.12.3 Calcium plus linoleic acid					
Herrera 1998	1/43	3/43		6.39%	0.33[0.04,3.08]
Herrera 2006	1/24	4/24		8.52%	0.25[0.03,2.08]
Subtotal (95% CI)	**67**	**67**		**14.9%**	**0.29[0.06,1.32]**
Total events: 2 (Calcium), 7 (Control)					
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.85); I²=0%					
Test for overall effect: Z=1.61(P=0.11)					
6.12.4 Calcium plus antioxidants					
Rumiris 2006	1/29	1/31		2.06%	1.07[0.07,16.31]
Subtotal (95% CI)	**29**	**31**		**2.06%**	**1.07[0.07,16.31]**
Total events: 1 (Calcium), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
Total (95% CI)	**426**	**428**		**100%**	**0.81[0.54,1.21]**
Total events: 38 (Calcium), 47 (Control)					
Heterogeneity: Tau²=0; Chi²=2.06, df=3(P=0.56); I²=0%					
Test for overall effect: Z=1.02(P=0.31)					
Test for subgroup differences: Chi²=2.03, df=1 (P=0.36), I²=1.33%					

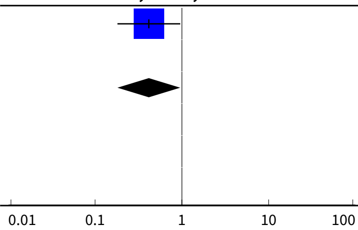


Comparison 7. High-dose (=/> 1 g) vs low-dose (< 1 g) calcium supplements

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pre-eclampsia	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.18, 0.96]
2 Preterm birth	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.09, 1.08]
3 Eclampsia	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.07, 1.53]
4 Stillbirth	1	262	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.13, 1.83]

Analysis 7.1. Comparison 7 High-dose (=/> 1 g) vs low-dose (< 1 g) calcium supplements, Outcome 1 Pre-eclampsia.

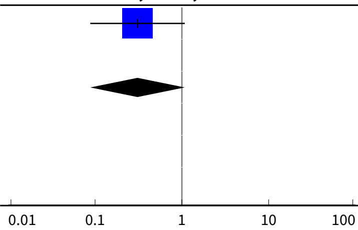
Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2013	7/123	19/139		100%	0.42[0.18,0.96]
Total (95% CI)	**123**	**139**		**100%**	**0.42[0.18,0.96]**
Total events: 7 (High dose), 19 (Low dose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.06(P=0.04)					



Favours high dose | Favours low dose

Analysis 7.2. Comparison 7 High-dose (=/> 1 g) vs low-dose (< 1 g) calcium supplements, Outcome 2 Preterm birth.

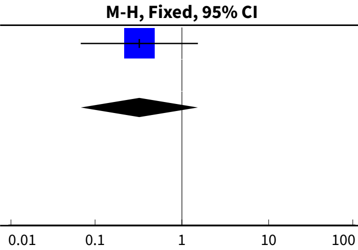
Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2013	3/123	11/139		100%	0.31[0.09,1.08]
Total (95% CI)	**123**	**139**		**100%**	**0.31[0.09,1.08]**
Total events: 3 (High dose), 11 (Low dose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.84(P=0.07)					



Favours high dose | Favours low dose

Analysis 7.3. Comparison 7 High-dose (=/> 1 g) vs low-dose (< 1 g) calcium supplements, Outcome 3 Eclampsia.

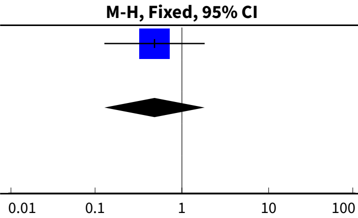
Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2013	2/123	7/139		100%	0.32[0.07,1.53]
Total (95% CI)	**123**	**139**		**100%**	**0.32[0.07,1.53]**
Total events: 2 (High dose), 7 (Low dose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					



Favours high dose | Favours low dose

Analysis 7.4. Comparison 7 High-dose (=/> 1 g) vs low-dose (< 1 g) calcium supplements, Outcome 4 Stillbirth.

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2013	3/123	7/139		100%	0.48[0.13,1.83]
Total (95% CI)	**123**	**139**		**100%**	**0.48[0.13,1.83]**
Total events: 3 (High dose), 7 (Low dose)					
Heterogeneity: Not applicable					



Favours high dose | Favours low dose

Study or subgroup	High dose n/N	Low dose n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.07(P=0.29)					
		Favours high dose	0.01 0.1 1 10 100	Favours low dose	

APPENDICES

Appendix 1. Search terms for ICTRP and ClinicalTrials.gov

ICTRP

antenatal AND calcium

prenatal OR calcium

pregnancy AND calcium

ClinicalTrials.gov

(Advanced search)

Intervention studies

calcium = intervention

pregnancy = condition

FEEDBACK

Stones, 7 December 2010

Summary

Noting that public health programs are now starting to include calcium supplementation, I wonder if the statements in the abstract and plain language summary that "there were no other clear benefits, or harms"/"No adverse effects have been found" should be revised to include mention of the increased risk of HELLP syndrome associated with calcium supplementation. At the very least it would prompt programmers to include surveillance and reporting for this life threatening complication and would help to clarify whether this is a real association.

(Feedback submitted by William Stones, December 2010)

Reply

We agree with the above feedback. We have added emphasis to the effect on HELLP syndrome to the discussion, and added to "Implications for practice":
"..........The increase in the risk of HELLP syndrome was small in terms of absolute numbers, and therefore we considered it to be outweighed by the overall reduction in death or severe morbidity; and to "Implications for research":
"The increase in the risk of HELLP syndrome identified by this review requires further investigation."

To the abstract results we have added "There was an anomalous increase in the risk of HELLP syndrome (two trials, 12,901 women: RR 2.67, 95% CI 1.05 to 6.82)."; and to the abstract conclusions we have added "We considered the latter benefit to outweigh the increase in HELLP syndrome, which was small in absolute numbers".

Contributors

Feedback: William Stones

Reply: G Justus Hofmeyr

Walkinshaw, 2 November 2010

Summary

I feel that the conclusion drawn for high-risk women go beyond the data. Five trials are cited for high-risk women. Of these one trial assessed risk by roll over test, another by roll over test plus angiotensin II infusion, and a third by roll over test plus at least one risk factor. All three of these trials excluded chronic medical conditions. For the two other trials, data for high-risk women come either from a subgroup analysis or are unpublished data. Villar 1990 includes mainly nulliparous women and excluded medical disease; L-Jaramillo 1990 includes nulliparous women and also excludes underlying medical disease. Thus three of the five trials do not describe high risk in any meaningfully clinically translatable way, and exclude the highest risk women (such as those with previous pre-eclampsia, chronic hypertension, or renal disease). The two additional studies also largely exclude clinical high-risk factors.

To draw a broad conclusion using the very impressive risk reduction in 'high risk' from this is not really translatable to clinical high risk. I think it will confuse clinicians, who will not look at the detail of the trials used and assume that high risk means the usual suspects, when it manifestly does not. The authors should consider some caveat to their conclusion. I actually think the current conclusion misleads.

During the genesis of the NICE guidance we looked in some detail at this to determine if there was evidence of benefit for clinically high-risk women, and concluded that at present those studies had not been performed. I do not feel that it is enough to rely on studies selecting women using research techniques to assess risk.

The issue in low-risk women is more contentious and I make no comment on that part.

(Summary of comment from Stephen Walkinshaw, Obstetrician and Chair of NICE guideline development group for Hypertension in Pregnancy, November 2010)

Reply

We agree with the points made, and have added the following to the results section: "Five studies enrolled women considered to be at high risk of pre-eclampsia. The definitions of high risk and the actual risk (rate of pre-eclampsia in the placebo group) were variable: positive 'roll-over test at 28-30 weeks (8/34) (L-Jaramillo 1990); teenagers 17 years or younger (3/88) (Villar 1990); positive 'roll-over' test at 28-32 weeks plus one clinical risk factor (7/15) (Niromanesh 2001); positive 'roll-over' and positive angiotensin II infusion test (15/34) (S-Ramos 1994); and nulliparous teenagers 17.5 years or younger (21/135) (L-Jaramillo 1997). The clinical usefulness of the pooled results in this subgroup is therefore limited." To the abstract we have added: "The varied methods of selecting women as being at high-risk limit the clinical usefulness of these pooled results."

Contributors

Feedback: Stephen Walkinshaw

Reply: G Justus Hofmeyr

WHAT'S NEW

Date	Event	Description
18 September 2017	New search has been performed	The search was updated and three new trials included (Asemi 2012; Asemi 2016; Khan 2013). A new comparison of high-dose versus low-dose calcium has been incorporated into this update.
18 September 2017	New citation required but conclusions have not changed	The review includes a total of 27 trials. The conclusions remain unchanged.

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 3, 1998

Date	Event	Description
24 May 2013	New citation required and conclusions have changed	Eleven studies have been included for this update (Almirante 1998; Bassaw 1998; Cong 1995; Herrera 1998; Herrera 2006; Jarjou 2004; Li 2000; Marya 1987; Rogers 1999; Rumiris 2006; Taherian 2002).Ten studies of low-dose calcium added. New meta-analyses performed. Substantially changed conclusions. Search updated in May 2014, six reports added to Studies awaiting classification (Asemi 2012b; Diogenes 2013; Goldberg 2013; Herrera 2006b; Jarjou 2013; Sulovic 2013a).
28 March 2013	New search has been performed	Search updated. Methods updated.
6 January 2011	Feedback has been incorporated	Feedback from William Stones and Stephen Walkinshaw added with replies from the authors.
5 July 2010	New citation required but conclusions have not changed	New author helped to update the review.
31 May 2010	New search has been performed	Search updated. Fifteen new reports identified: one new study (Kumar 2009) included and four new trials excluded (de Souza 2006; Dizavandy 1998; Herrera 1998a; Karandish 2003).
31 October 2009	Amended	Search updated. Fourteen new reports added to Studies awaiting classification.
1 September 2008	Amended	Converted to new review format.
2 March 2006	New search has been performed	Search updated.
2 March 2006	New citation required and conclusions have changed	A large trial of calcium supplementation in communities with low dietary calcium intake has been added (WHO 2006).

CONTRIBUTIONS OF AUTHORS

Álvaro Atallah and Justus Hofmeyr prepared the protocol for the initial Cochrane Review.
Justus Hofmeyr prepared the data analysis for the initial Cochrane Review and is primarily responsible for maintaining the review, with input from the other authors. Tess Lawrie prepared the first draft of the 2010 update of the review with input from Justus Hofmeyr and Álvaro Atallah.

Justus Hofmeyr prepared the protocol revision and the first draft of the text for the 2013 update. Justus Hofmeyr and Regina Torloni performed the study selection and data extraction for the 2013 update. Justus Hofmeyr contributed to the analysis and writing of the 2018 revision. All authors gave input and approved the final version of the 2018 revision.

DECLARATIONS OF INTEREST

G Justus Hofmeyr: Justus Hofmeyr was a collaborator in the WHO Calcium Trial (WHO 2006), which was included in this review and did not participate in the decision on inclusion and data extraction for this study

Theresa A Lawrie: none known.

Álvaro N Atallah: none known.

Maria Regina Torloni: Maria Regina Torloni is investigator for an ongoing study (Torloni 2015) which may potentially be included in future updates of this review

SOURCES OF SUPPORT

Internal sources

- Universidade Federal de Sao Paulo/Escola Paulista de Medicina, Brazil.
- Medical Research Council, UK.
- Department for International Development, UK.
- (GJH) Effective Care Research Unit, University of the Witwatersrand/Fort Hare, Eastern Cape Department of Health, South Africa.

External sources

- UNDP/UNFPA/WHO/World Bank (HRP), Switzerland.
- NHS Programme for Research and Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The subgroup analysis for high-dose calcium of both dietary calcium and study size was not prespecified in the original protocol. In October 2004 we added seven additional outcomes (marked * below). For the 2014 update we added two outcome measures, marked ** below, in order to include newly published data. As such, these should be regarded as post-hoc analyses, and interpreted with caution.

In 2014 we added a new comparison: low-dose calcium supplementation, with or without cointerventions, versus no supplementation. In 2018 we added an additional comparison: high-dose versus low-dose calcium supplementation.

Secondary outcomes

For the woman

1. *Proteinuria.
2. *Severe pre-eclampsia as defined by trial authors.
3. *Eclampsia.
4. *HELLP syndrome.
5. *Intensive care unit admission.
6. *Maternal death.
7. ** Miscarriage.

For the child

1. *Death or severe neonatal morbidity.
2. **Dental caries in childhood (one or more decayed, missing or filled teeth, or as defined by trial authors).

The methods section for this review, Criteria for considering studies for this review, was updated in 2012.

Amendments 2014

We made the following amendments for the 2014 review.

1. We included a separate analysis for trials with less than 1 g of calcium daily.
2. If there were insufficient high-quality randomised placebo-controlled trials of low-dose calcium alone to provide robust evidence of effectiveness, we separately reviewed additional evidence from lower quality studies, with appropriate caution in the interpretation of the results:
   a. quasi-randomised trials (by alternation, unstated method of allocation or other quasi-random methods);
   b. trials without placebo control;
   c. trials of calcium plus additional supplements (e.g. vitamin D, linoleic acid, or anti-platelet agents).

We included subgroup analysis by trial quality and cointerventions.

In 2018, we added in an additional search of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP).

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Calcium [*administration & dosage]; Hypertension [mortality] [*prevention & control]; Linoleic Acid [administration & dosage]; Pre-Eclampsia [mortality] [*prevention & control]; Pregnancy Complications, Cardiovascular [mortality] [*prevention & control]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Vitamin D [administration & dosage]; Vitamins [administration & dosage]

MeSH check words

Female; Humans; Pregnancy