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

Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L, Torloni MR

Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L, Torloni MR.
Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems.
Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD001059.
DOI: 10.1002/14651858.CD001059.pub4.

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[Intervention Review]

Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

G Justus Hofmeyr[1], Theresa A Lawrie[2], Álvaro N Atallah[3], Lelia Duley[4], Maria R Torloni[3]

[1]Department of Obstetrics and Gynaecology, East London Hospital Complex, University of the Witwatersrand, University of Fort Hare, Eastern Cape Department of Health, East London, South Africa. [2]Cochrane Gynaecological Cancer Group, Royal United Hospital, Bath, UK. [3]Brazilian Cochrane Centre, Centro de Estudos de Medicina Baseada em Evidências e Avaliação Tecnológica em Saúde, São Paulo, Brazil. [4]Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Nottingham, UK

Contact address: G Justus Hofmeyr, Department of Obstetrics and Gynaecology, East London Hospital Complex, University of the Witwatersrand, University of Fort Hare, Eastern Cape Department of Health, Frere and Cecilia Makiwane Hospitals, Private Bag X 9047, East London, Eastern Cape, 5200, South Africa. justhof@gmail.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 6, 2014.

Citation: Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD001059. DOI: 10.1002/14651858.CD001059.pub4.

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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.

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 the Cochrane Pregnancy and Childbirth Group's Trials Register (28 March 2013) and contacted study authors for more data where possible. We updated the search in May 2014 and added the results to the 'Awaiting Classification' section of the review.

Selection criteria

Randomised controlled trials (RCTs) comparing high-dose (at least 1 g daily of calcium) or low-dose calcium supplementation during pregnancy with placebo or no calcium.

Data collection and analysis

We assessed eligibility and trial quality, extracted and double-entered data.

Main results

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

We included 14 studies in the review, however one study contributed no data. We included 13 high-quality studies in our meta-analyses (15,730 women). The average risk of high blood pressure (BP) was reduced with calcium supplementation compared with placebo

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(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 significant reduction in the risk of pre-eclampsia associated with calcium supplementation (13 trials, 15,730 women: RR 0.45, 95% CI 0.31 to 0.65; I^2 = 70%). The effect was greatest 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%) and women at high risk of pre-eclampsia (five trials, 587 women: average RR 0.22, 95% CI 0.12 to 0.42; I^2 = 0%). These data should be interpreted with caution because of the possibility of small-study effect or publication bias.

The composite outcome maternal death or serious morbidity was reduced (four trials, 9732 women; RR 0.80, 95% CI 0.65 to 0.97; I^2 = 0%). Maternal deaths were not significantly different (one trial of 8312 women: calcium group one death versus placebo group six deaths). There was an anomalous increase in the risk of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome (two trials, 12,901 women: RR 2.67, 95% CI 1.05 to 6.82; I^2 = 0%) in the calcium group, however, the absolute number of events was low (16 versus six).

The average risk of preterm birth was reduced in the calcium group (11 trials, 15,275 women: RR 0.76, 95% CI 0.60 to 0.97; I^2 = 60%) and amongst women at high risk of developing pre-eclampsia (four trials, 568 women: average RR 0.45, 95% CI 0.24 to 0.83; I^2 = 60%), but no significant reduction in neonatal high care admission. There was no overall 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; I^2 = 0%).

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)

We included 10 trials (2234 women) that evaluated low-dose supplementation with calcium alone (4) or in association with vitamin D (3), linoleic acid (2), or antioxidants (1). 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 significantly reduced the risk of pre-eclampsia (RR 0.38, 95% CI 0.28 to 0.52; I^2 = 0%). There was also a reduction in hypertension, low birthweight and neonatal intensive care unit admission.

Authors' conclusions

Calcium supplementation (≥ 1 g/day) is associated with a significant reduction in the risk of pre-eclampsia, particularly for women with low calcium diets. The treatment effect may be overestimated due to small-study effects or publication bias. It also reduces preterm birth and the occurrence of the composite outcome 'maternal death or serious morbidity'. We considered these benefits to outweigh the increased risk of HELLP syndrome, which was small in absolute numbers. The World Health Organization recommends calcium 1.5 g to 2 g daily for pregnant women with low dietary calcium intake.

The limited evidence on low-dose calcium supplementation suggests a reduction in pre-eclampsia, but needs to be confirmed by larger, high-quality trials. Pending such results, in settings of low dietary calcium where high-dose supplementation is not feasible, the option of lower-dose supplements (500 to 600 mg/day) might be considered in preference to no supplementation.

PLAIN LANGUAGE SUMMARY

Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

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.

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. The review of 24 trials found good quality evidence that calcium supplementation with high doses (at least 1 g daily) during pregnancy (13 studies involving 15,730 women) is a safe and relatively cheap 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 were also less likely to die or have serious problems related to pre-eclampsia. Babies were less likely to be born preterm. No adverse effects have been found but further research is needed into the ideal dosage of supplementation.

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Limited evidence from 10 trials (2234 women) suggested that a relatively low dose may be effective although co-interventions such as vitamin D, linoleic acid or antioxidants were given in six of the included trials.

In settings of low dietary calcium where high-dose supplementation is not feasible, the option of lower dose supplements (500 to 600 mg/day) might be considered in preference to no supplementation.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

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		**RR 0.45** (0.31 to 0.65) **RR 0.36** (0.20 to 0.65) **RR 0.22** (0.12 to 0.42)	15,730 (13) 10,678 (8) 587 (5)	⊕⊕⊕⊕ **high** ⊕⊕⊕⊕ **high** ⊕⊕⊕⊕ **high**	P < 0.0001 P = 0.0007 P < 0.00001
	65 per 1000	29 per 1000 (20 to 42)				
	Low calcium diet					
	57 per 1000	21 per 1000 (11 to 37)				
	High-risk women					
	176 per 1000	38 per 1000 (21 to 74)				
Preterm birth	Overall		**RR 0.76** (0.60 to 0.97)	15,275 (11)	⊕⊕⊕⊕ **high**	P = 0.03
	104 per 1000	79 per 1000 (62 to 101)				
HELLP Syndrome	1 per 1000	3 per 1000	**RR 2.67** (1.05 to 6.82)	12,904 (2)	⊕⊕⊕⊕ **high**	P = 0.04

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.

CI: confidence interval
HELLP: haemolysis, elevated liver enzymes and low platelets
RR: risk ratio

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BACKGROUND

Description of the condition

High blood pressure, with or without proteinuria, is a major causes 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 accounting 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).

Preterm birth, spontaneous and medically induced, 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 et al (Villar 1998).

During early pregnancy, blood pressure normally falls, climbing 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 mmHg or systolic 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 dL) (NHBPEP 2000) usually indicate the presence of pre-eclampsia. Recently, 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).

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 cheap, 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 (Carroli 1994; Duley 1995) 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. A subsequent systematic review (Bucher 1996) came to more enthusiastic conclusions, 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 to 2 g elemental calcium daily for

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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 to 2 g of calcium daily, and there was little robust evidence regarding smaller dosages.

2. The dosage of 1.5 to 2 g calcium daily is well above the daily recommended dietary calcium of 1 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 2004a) 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 of 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 protocol to include lower quality studies (e.g. quasi-randomised trials) of lower dosage studies only.

OBJECTIVES

To determine, from the best available evidence, the effect of calcium supplementation during pregnancy on the risk of high blood pressure and related maternal and fetal or neonatal adverse 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 trials with random allocation to calcium supplementation during pregnancy versus placebo. We included trials that were presented only as abstracts if there was sufficient detail (published and unpublished) to confirm that they were methodologically adequate. For the original review we excluded quasi-random designs. However, for this updated review 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, with appropriate caution in the interpretation of the results.

Types of participants

Pregnant women, regardless of the risk of hypertensive disorders of pregnancy. We excluded women with diagnosed hypertensive disorders of pregnancy.

Prespecified subgroups to be compared.

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 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

Supplementation with calcium from at the latest 34 weeks of pregnancy compared with placebo treatment. We excluded studies with no placebo. We limited the initial analysis to intended supplementation with at least 1 g of calcium per day. Future updates of this review would include an analysis of effect by dosage, including lower dosage regimens. For the 2012 update of the review, we included trials of calcium less than 1 g daily plus additional supplements (e.g. vitamin D, linoleic acid, or anti-platelet agents).

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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 this 2013 update we have 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 will be 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 will be a composite outcome of death or at least one measure of serious morbidity. In addition each individual outcome will be presented.
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 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 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.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (28 March 2013). We updated the search in May 2014 and added the results to Studies awaiting classification.

The Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

For details of searches carried out in the previous version of the review, *see* Appendix 1.

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We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the 2010 update, *see* Appendix 2.
For the 2013 update, we have used the following methods when assessing the trials identified by the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies that we identified as a result of the search strategy. For the 2013 update, this was performed by GJH and MRT. We resolved any disagreement through discussion or, if required, by consulting L Duley (LD).

Data extraction and management

We designed a form to extract data. For eligible studies, GJH and MRT extracted data for the 2013 version . We resolved discrepancies through discussion or, if required, by consulting LD. We entered data into Review Manager software (RevMan 2012) and checked it for accuracy.
When study information and/or data were unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

TAL, MRT and GJH independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2011*).* We resolved any disagreement by discussion or by involving a third assessor.

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

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

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

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

We described for each included study 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:

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

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

We described for each included study 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 would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

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

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

We described for each included study 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:

- 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)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state 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 re-included missing data in the analyses which we undertook.
We assessed the methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups; $\leq$ 20% participants missing);
- 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; > 20% participants missing);
- unclear risk of bias.

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If it was not possible to enter data based on intention-to-treat or 20% or more participants were excluded from the analysis of that outcome, then the trial was excluded.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other 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* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference for outcomes measured in the same way between trials. In future updates, if appropriate, we plan to use the standardised mean difference to combine trials that measure the same outcome but used different methods.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials would have been included in the analyses along with individually-randomised trials. We would have adjusted their sample sizes using the methods described in the *Handbook* (Higgins 2011) (section 16.3.4) using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we had used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually-randomised trials, we would have synthesised the relevant information. We would consider it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely. We would acknowledge heterogeneity in the randomisation unit and perform sensitivity analyses to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, 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, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. 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 the Tau^2 was greater than zero and either an I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

We investigated reporting biases (such as publication bias) by doing a subgroup analysis and funnel plot based on the sample sizes of the trials.

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Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). 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 was treated as the average of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

When we used random-effects analyses, the results are presented as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

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 sizes.

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

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012). 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 undertook sensitivity analysis by considering the results of the larger sample size trials versus the overall results for primary outcomes.

RESULTS

Description of studies

Please see Included studies below.

Compliance, where reported, was generally > 80% (Belizan 1991 84% and 86% for calcium and placebo; WHO 2006 84.5% and 86.2%; S-Ramos 1994 79% and 81%). However, in CPEP 1997 compliance was 64% and 67% and in Crowther 1999 31% and 24% of women stopped taking the tablets before the end of the trial. In L-Jaramillo 1997 2 women were withdrawn for non-compliance.

Results of the search

The search strategy identified 49 studies, of which we included 24. (Seven trial reports are awaiting classification. *See*: Studies awaiting classification).

Included studies

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

We included 14 studies in the review, however one study (Jarjou 2004) contributed no data. Of the remaining 13 studies, four were multicentre studies: one 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.

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.

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

We included 10 studies: four investigated calcium supplementation alone (Almirante 1998; Bassaw 1998; Cong 1995; Rogers 1999); three investigated calcium plus vitamin D (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). Please see Characteristics of included studies for further details.

Excluded studies

We excluded 25 studies from the review (Characteristics of excluded studies).

Risk of bias in included studies

See table of Characteristics of included studies and Figure 1, Figure 2.

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Figure 1. 'Risk of bias'[summary: review authors' judgements about each risk of bias item for each included study.

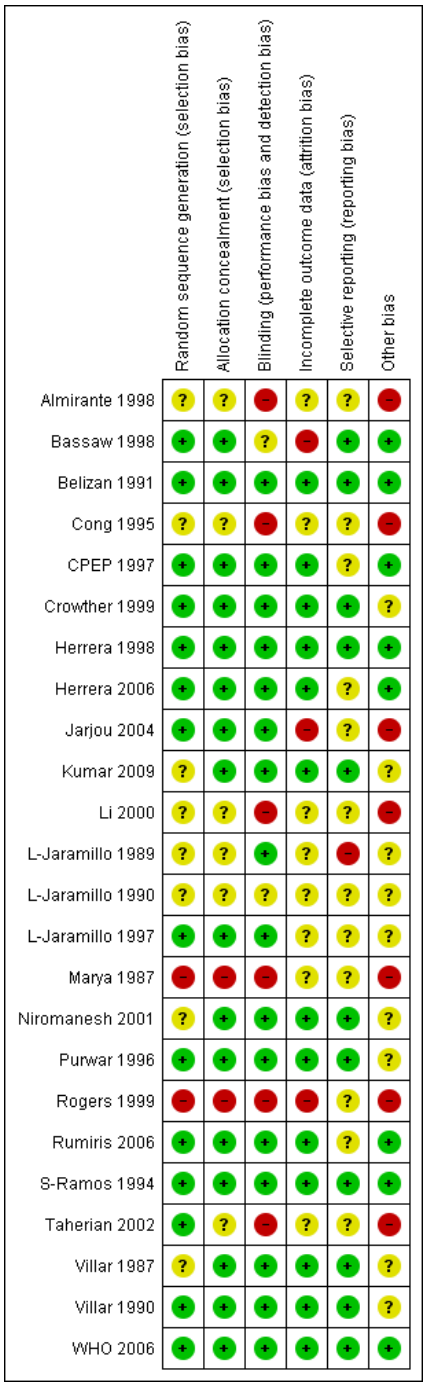

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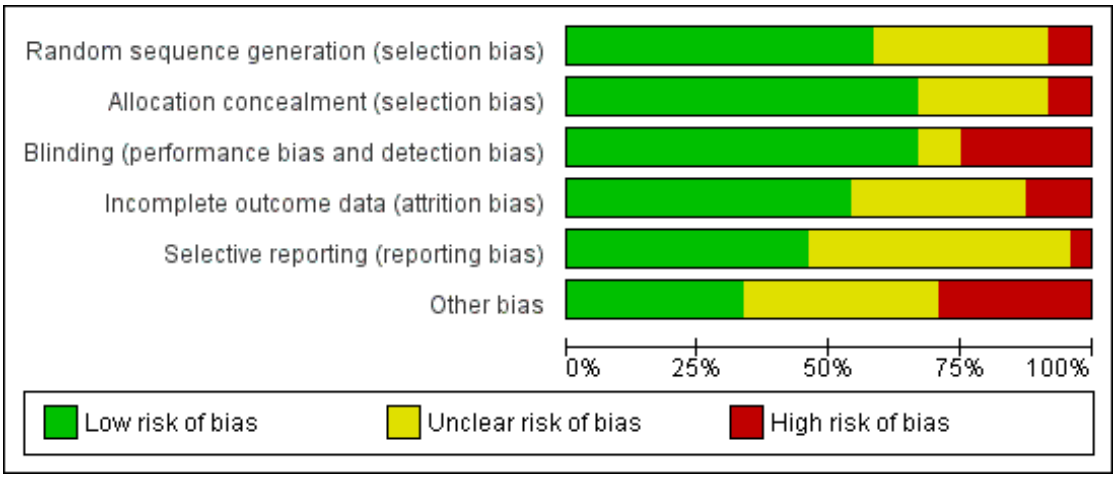
Figure 2. 'Risk of bias'[graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



High-dose calcium supplementation

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 is not explained. In Kumar 2009, we contacted the authors to clarify the imbalance in group size that occurred in their study. We accept their 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 a low risk of bias (Bassaw 1998; Herrera 1998; Herrera 2006; Rumiris 2006) and six to be at a high risk of bias (Almirante 1998; Cong 1995; Li 2000; Marya 1987; Rogers 1999; Taherian 2002). We considered the latter studies to be at a high risk because they were either quasi-randomised or not clearly randomised studies.

Effects of interventions

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

High-dose calcium supplementation

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 more extreme results than 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.

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 significantly 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).

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The reduction in RR was greatest for the small trials (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), for women at high risk of developing pre-eclampsia (four trials, 327 women: average RR 0.47, 95% CI 0.22 to 0.97; Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 11.01$, df = 3 (P = 0.01); $I^2 = 73\%$; Analysis 2.1.2), 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). Assymetric funnel plots for these analyses (Figure 3, Figure 4, Figure 5) suggest that the treatment effect may be overestimated due to small-study effects or publication bias.

Figure 3. 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).

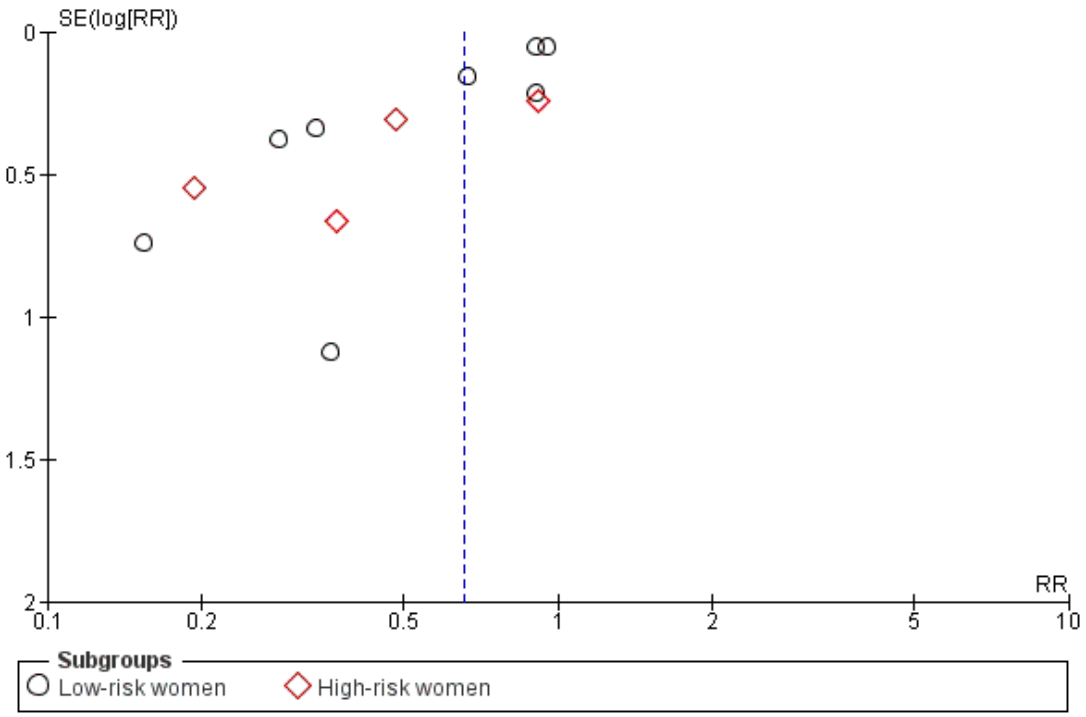

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Figure 4. Funnel plot of comparison: 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, outcome: 1.1 High blood pressure (with or without proteinuria).

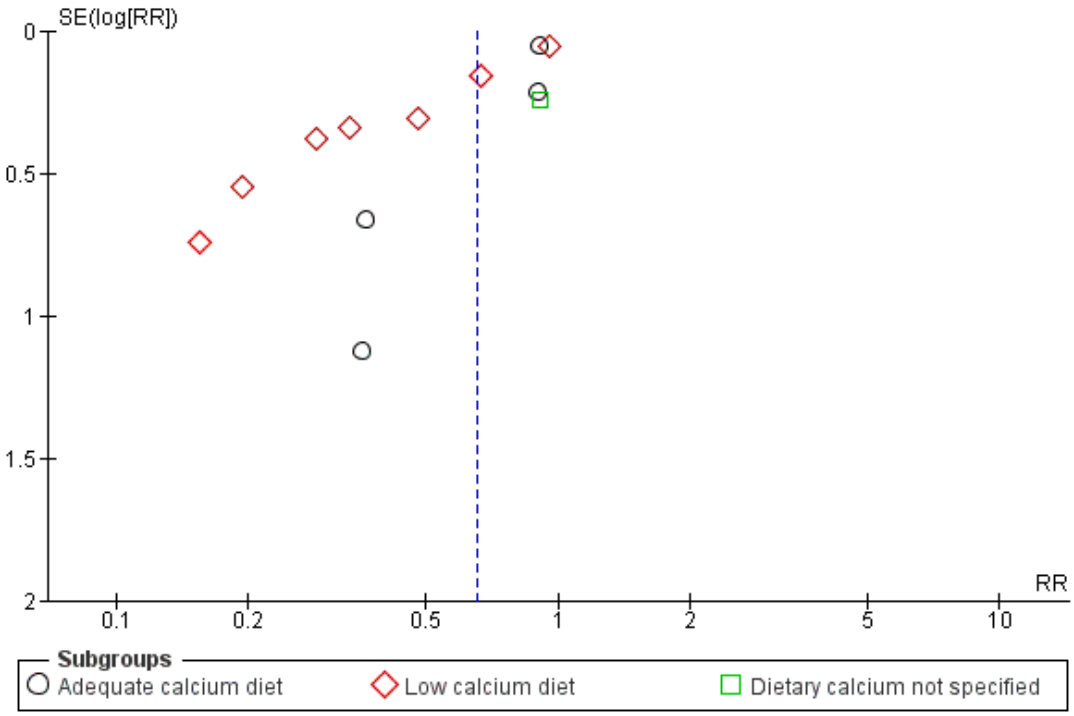

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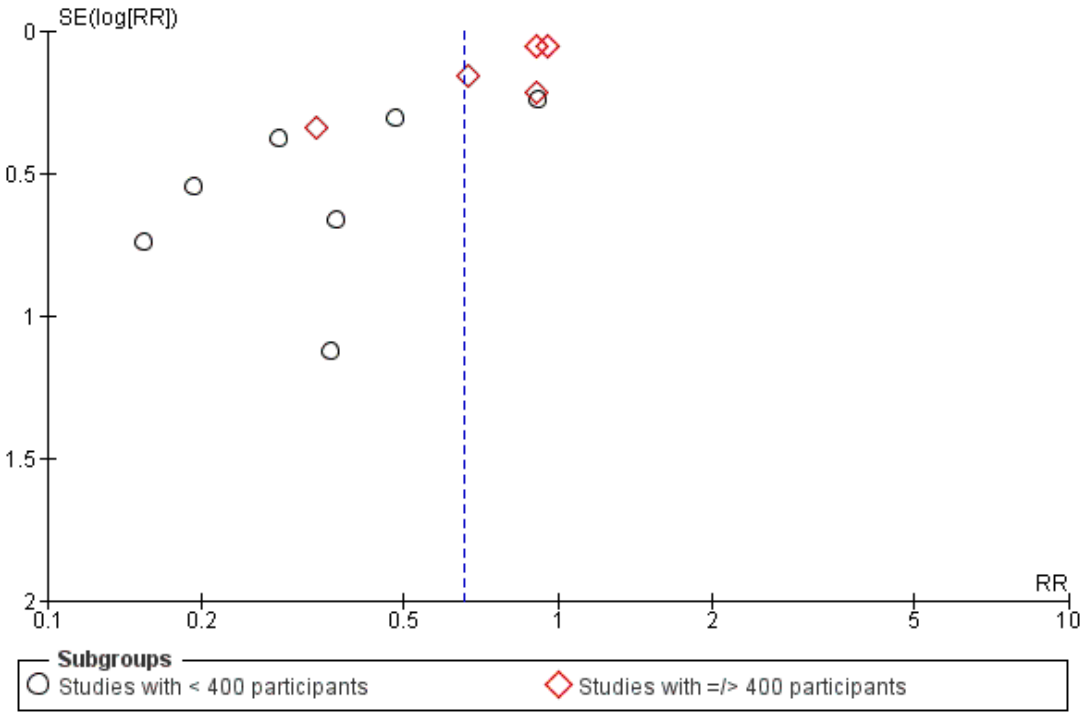
Figure 5. Funnel plot of comparison: 3 Routine high-dose calcium supplementation in pregnancy by study sample size, outcome: 3.1 High blood pressure (with or without proteinuria).



(2) Pre-eclampsia

Overall, there was a significant reduction in the average risk of pre-eclampsia (13 trials, 15,730 women: RR 0.45, 95% CI 0.31 to 0.65 Heterogeneity: Tau² = 0.20; Chi² = 40.31, df = 12 (P < 0.0001; I² = 70%) Analysis 1.2. This reduction in risk ratio 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), and 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. Test for subgroup differences: Chi² = 2.73, df = 2, P = 0.26, I² = 26.8%). Assymetric funnel plots for these analyses (Figure 6, Figure 7) suggest that the treatment effect may be overestimated due to small-study effects or publication bias. 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.

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Figure 6. Funnel plot of comparison: 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, outcome: 1.2 Pre-eclampsia.

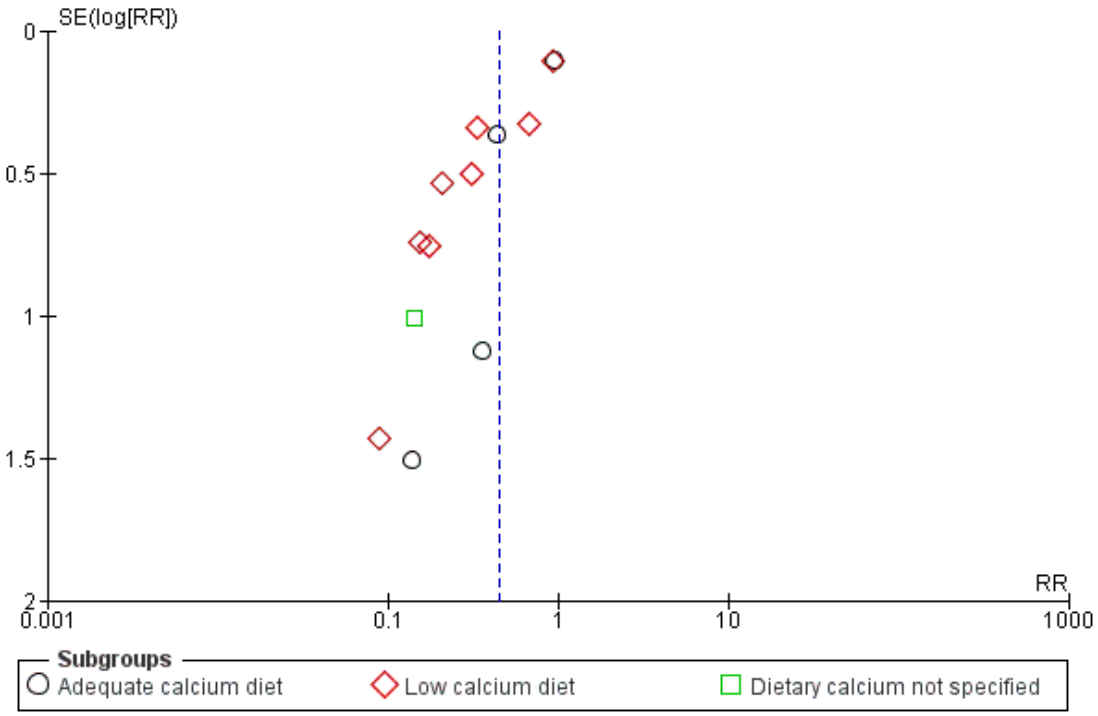

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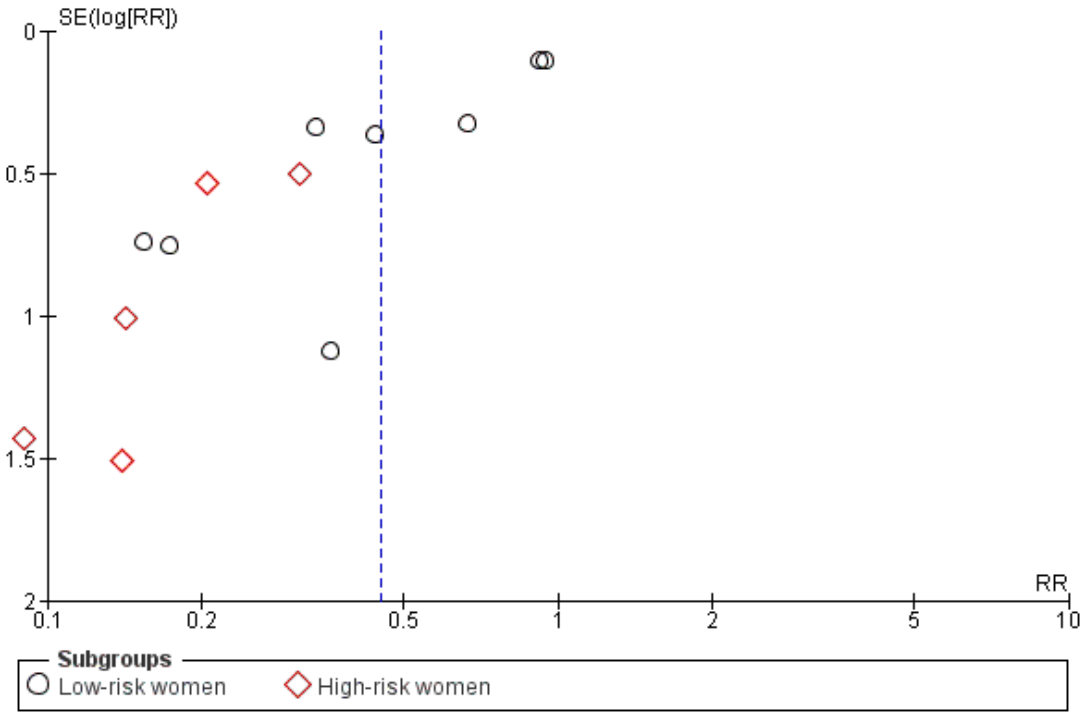
Figure 7. Funnel plot of comparison: 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, outcome: 2.2 Pre-eclampsia.



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 0.26 for the adequate calcium trials, and in the large studies 0.63 and 0.70 respectively; Analysis 4.1, Figure 8), Test for subgroup differences: $Chi^2 = 10.28$, df = 4 (P = 0.04), $I^2 = 61.1\%$).

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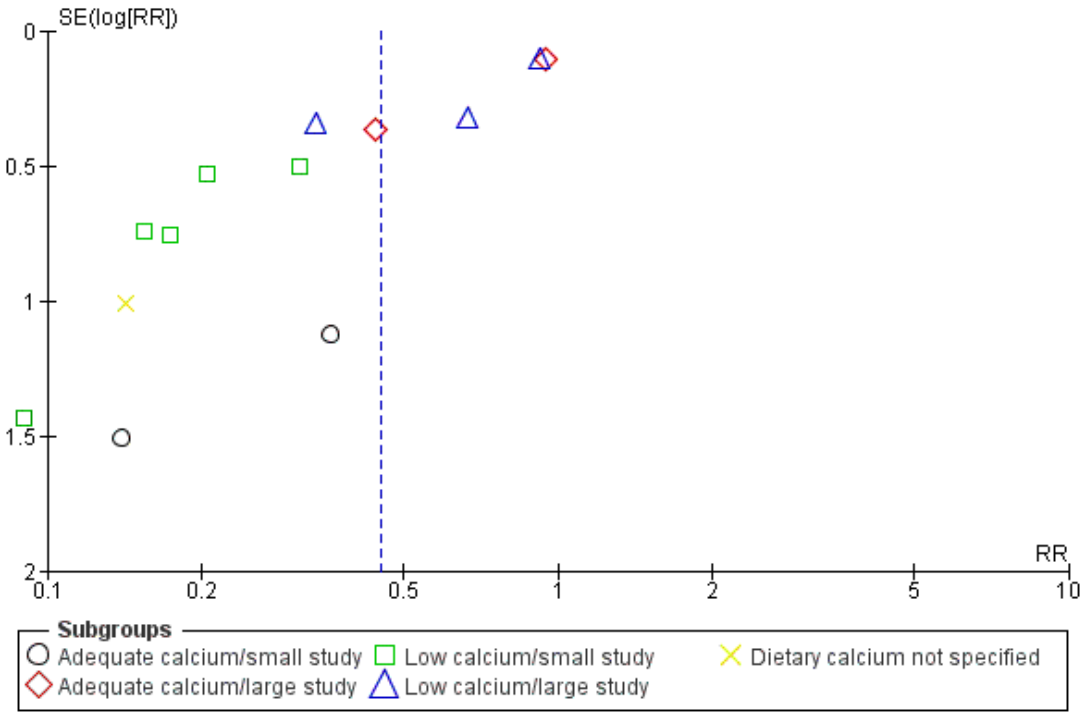
Figure 8. Funnel plot of comparison: 4 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium and study sample size (not pre-specified), outcome: 4.1 Pre-eclampsia.



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 with calcium versus 3/88 with placebo).

(3) Preterm birth

Calcium supplementation significantly reduced the average risk of preterm birth overall (11 trials 15,275 women: RR 0.76, 95% CI 0.60 to 0.97; 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. Assymetric funnel plots for these analyses (Figure 9, Figure 10, Figure 11) suggest that the treatment effect may be overestimated due to small-study effects or publication bias. 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.

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Figure 9. Funnel plot of comparison: 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, outcome: 1.3 Preterm birth.

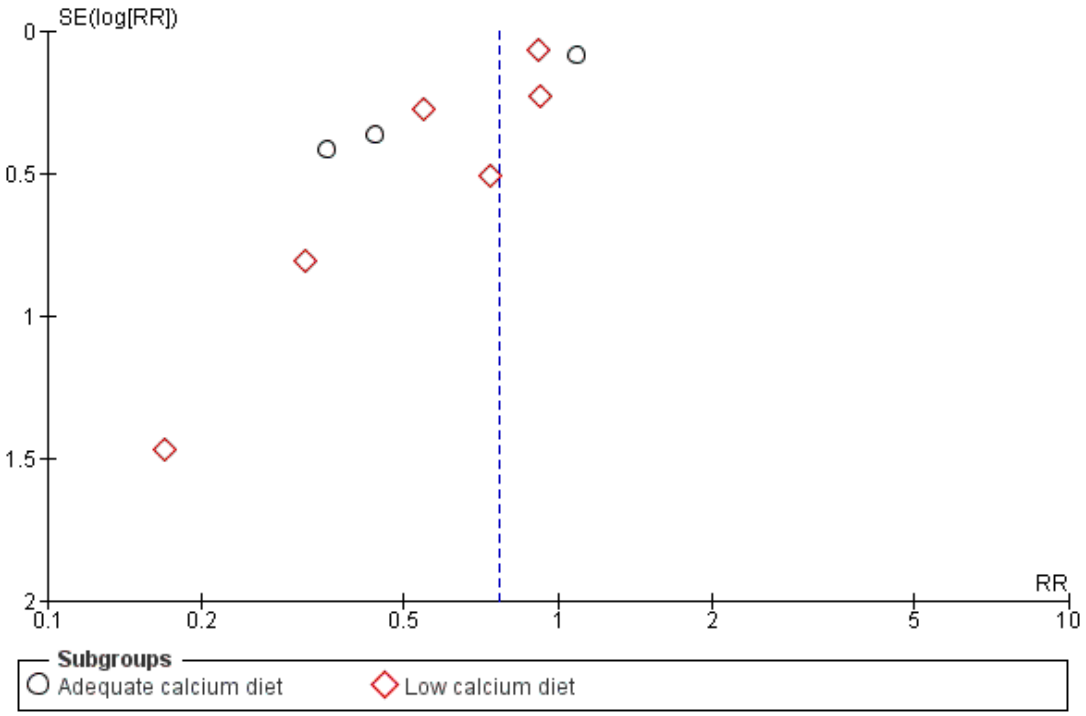

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Figure 10. Funnel plot of comparison: 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, outcome: 2.3 Preterm birth.

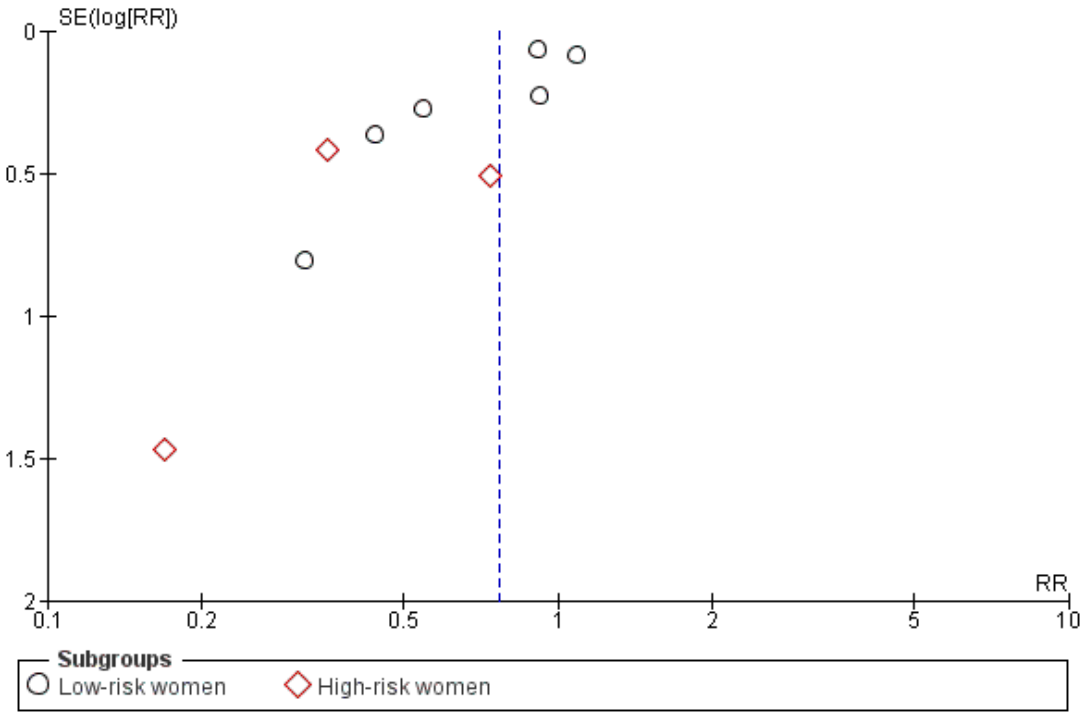

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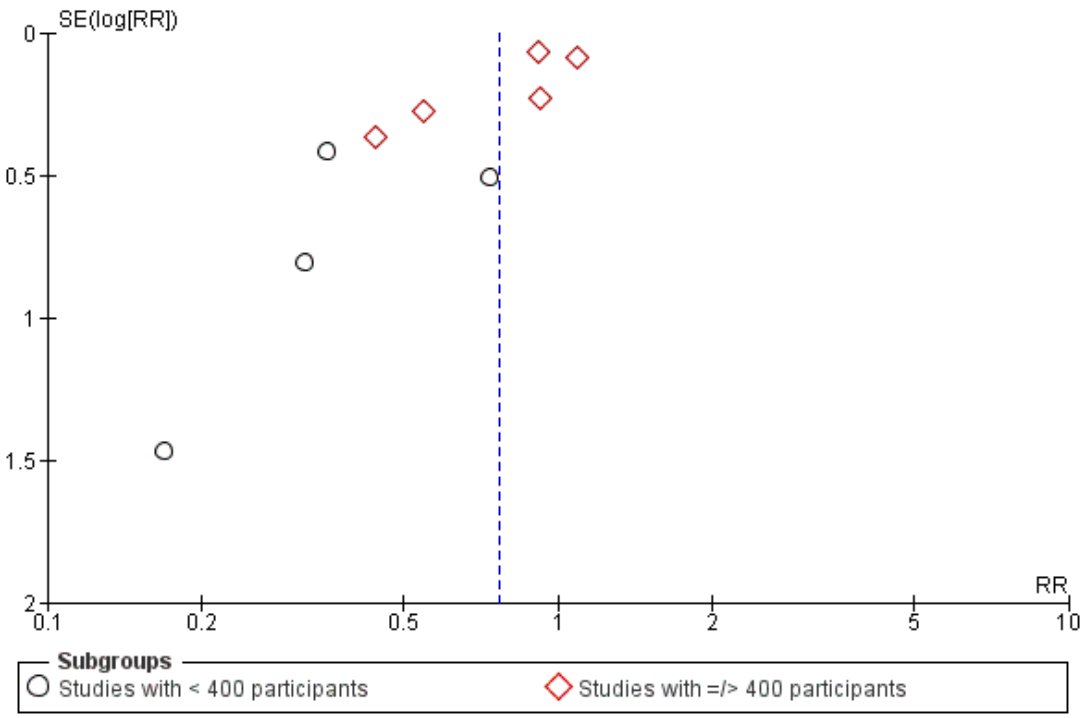
Figure 11. Funnel plot of comparison: 3 Routine high-dose calcium supplementation in pregnancy by study sample size, outcome: 3.3 Preterm birth.



(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: Chi² = 2.83, df = 3 (P = 0.42); I² = 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: Chi² = 1.46, df = 5 (P = 0.92); I² = 0%; Analysis 1.5).

Secondary outcomes

(6) Maternal death or serious morbidity

The risk of 'maternal death or serious morbidity' was significantly reduced for women allocated calcium supplementation compared with placebo (four trials, 9732 women: RR 0.80, 95% CI 0.65 to 0.97; Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%; Analysis 1.6). It should be noted that virtually 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: Chi² = 0.91, df = 2 (P = 0.63); I² = 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: Chi² = 5.21, df = 7 (P = 0.63); I² = 0%; Analysis 1.8), although the upper confidence limit just crossed the line of no effect.

(9) *Proteinuria

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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; 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). One death occurred in the calcium group and six in the placebo group, a difference which was not statistically significant (RR 0.17, 95% CI 0.02 to 1.39; Analysis 1.14).

(15) Mother's hospital stay seven days or more

Data were not available for this outcome.

(16) 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.

(17) Neonate small-for-gestational age

There was no overall effect on the risk ratio 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).

(18) Neonate in intensive care unit seven days or more

Data were not available for this outcome.

(19) *Death or severe neonatal morbidity

No data were available for this outcome.

(20) Childhood disability

Data were not available for this outcome.

(21) 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 significantly 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 (calcium group mean 646 mg, standard deviation (SD) 396, placebo group 642, SD 448 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 (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 the Crowther 1999 trial, 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 the CPEP 1997 study 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) limit 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.

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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.

(22) Childhood diastolic blood pressure > 95th percentile

Data were available only from the Belizan 1991 study. The difference was not statistically significant (Analysis 1.18).

(23) Childhood dental caries

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).

Low-dose calcium supplementation

Primary outcomes

(1) High blood pressure with or without proteinuria

High blood pressure was significantly reduced 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 with calcium supplementation alone (558 women, RR 0.57, 95% CI 0.39 to 0.82;) and one with calcium plus linoleic acid (48 women, RR 0.20; 95% CI 0.05 to 0.82).

(2) Pre-eclampsia

Pre-eclampsia was reduced but not statistically significantly in one trial of low-dose calcium supplementation alone with low risk of bias (Bassaw 1998: 171 women, RR 0.30, 95% CI 0.06 to 1.38). The point estimate was consistent with those of all nine trials that reported this outcome (2234 women, RR 0.38, 95% CI 0.28 to 0.52. Analysis 6.8). The reduction was also consistent across the subgroups: calcium alone (four studies, one with low risk of bias: 980 women, RR 0.36, 95% CI 0.23 to 0.57;); calcium plus linoleic acid (two studies with low risk of bias: 134 women, RR 0.23, 95% CI 0.09 to 0.60); calcium plus vitamin D, (two studies with high risk of bias: 1060 women, RR 0.49, 95% CI 0.31 to 0.78) and a trend 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 = 2.66, df = 3, P = 0.45, I^2 = 0%.

(3) Preterm birth

Preterm birth was significantly reduced in one study of calcium supplementation alone (422 women, average RR 0.40, 95% CI 0.21 to 0.75, Analysis 6.2), but as it was not reported in the other three studies of calcium supplementation alone, the possibility of publication bias needs to be considered. Overall, there was no effect on preterm birth in four studies (1190 women, average RR 0.67; 95% CI 0.24 to 1.87; Heterogeneity: Tau^2 = 0.67; Chi^2 = 12.99, df = 3 (P = 0.005); I^2 = 77%), Analysis 6.2.

(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 may be due to publication bias (422 women, RR 0.44; 95% CI 0.20 to 0.99; Analysis 6.3).

(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 6.4).

Secondary outcomes

(6) Placental abruption

One study reported this outcome and the numbers were too small for meaningful analysis (Analysis 6.5).

(7) Caesarean section

Caesarean section was significantly 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% Analysis 6.6), 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%).

(8) Severe pre-eclampsia

Two trials reported severe pre-eclampsia and there was no clear difference between the groups (146 women: RR 0.34, 95% CI 0.10 to 1.31; Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 = 0%; Analysis 6.7).

(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).

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(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 trend to reduced miscarriage in the calcium plus antioxidant group (60 women, RR 0.06, 95% CI 0.00 to 1.04; Analysis 6.10).

(11) Birthweight less than 2500 g

The risk of having a baby with birthweight less than 2500 g was significantly reduced in two studies of calcium supplementation plus linoleic acid (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).

DISCUSSION

Summary of main results

High-dose calcium supplementation

Calcium supplementation with at least 1 g of calcium approximately halves the risk of pre-eclampsia, 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 for which this was not statistically significant. Nevertheless, the point estimate for this subgroup of women was a 38% risk reduction. The greatest risk reduction was for women at high risk (variably defined; 78% reduction) and those with low baseline dietary calcium intake (64% reduction).

There was also a 35% reduction in the risk of gestational hypertension, with the greatest effect also amongst women at high risk and those with low calcium diets. These data should be interpreted with caution because of the possibility of small-study effect 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 HELLP syndrome was increased; however the absolute number of events was low (2.5/1000 versus 0.9/1000). There are no clear effects on other relevant outcomes at discharge from hospital. There are no clear differences in 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 (Figure 5, Figure 8).

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 large reduction in pre-eclampsia which was consistent between studies with low and high risk of bias. Results for calcium plus other interventions were similar to those for calcium alone, but the possibility that co-interventions 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.

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 calcium reduced the risk of pre-eclampsia, it did not translate into significant reductions in the risk of severe pre-eclampsia, eclampsia, or admission to intensive care. Nevertheless, the point estimates for these outcomes favoured calcium supplementation, and so moderate reductions in these outcomes remain possible.

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

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antepartum hospital admissions and fewer inductions of labour. However, these trials do not provide data on these outcomes.

This 2013 update has included data from trials using less than 1 g calcium daily (mostly 500 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, preterm birth and HELLP syndrome to be of a high quality (see Summary of findings for the main comparison).

In general, heterogeneity of findings seemed to be largely associated with study size, with the small studies having the most positive results (*see* Figure 9, Figure 10, Figure 11). 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

To our knowledge, there were no biases in the review process.

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.

Finally, 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.

AUTHORS' CONCLUSIONS

Implications for practice

The reduction in hypertension, pre-eclampsia and preterm birth, and in the composite outcome 'maternal death or severe morbidity' with high-dose calcium supplementation support the use of calcium supplementation during pregnancy, particularly for those with low dietary intake or high risk of pre-eclampsia. Implementation may be subject to competing priorities in low-resource settings. The increase in the risk of HELLP syndrome was small in terms of absolute numbers. Therefore, we consider it to be outweighed by the overall reduction in death or severe morbidity.

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

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 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).

In settings in which the recommended dosage of 1.5 to 2 g daily is not feasible, using a lower dose, rather than nothing, seems to

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be a reasonable interim approach. Revision of existing guidelines should include consideration of the data on low-dosage supplementation, evidence on potential risk and supplement interactions, and logistic and cost implications.

Implications for research

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. Robust research is needed to confirm the beneficial effects found in the limited evidence on the use of less than one gram of calcium daily. 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. Research into the effects of calcium supplementation combined with low-dose aspirin would be of value.

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 confirmed by 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 (*Calcium supplementation commencing before pregnancy, or food fortification with calcium, for preventing hypertensive disorders of pregnancy - Cochrane protocol in progress 2013)*. We are currently testing this hypothesis in a double-blind randomised trial of supplementation with 500 mg calcium commencing before pregnancy in women with previous pre-eclampsia (Hofmeyr 2011). If found to be effective, the next research step will be community supplementation with staple food fortification.

ACKNOWLEDGEMENTS

We thank the trial authors who have contributed additional data for this review. We also thank Maria Kalousi and Oliver Boothroyd for their assistance with the translation of certain articles to English, and the Cochrane Pregnancy and Childbirth Group team for administrative support.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

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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
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**
Random sequence generation (selection bias)	Unclear risk	Not specified.
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and 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.

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 body mass index. 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

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Bassaw 1998 (*Continued*)

Participants	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
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 $\geq$ 140/90 mmHg), pre-eclampsia (hypertension plus proteinuria)
Notes	8 participants were unavailable for analysis.

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 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 (performance bias and detection 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
Incomplete outcome data (attrition bias) All outcomes	High risk	8 participants were unavailable for analysis.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.

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Bassaw 1998 (*Continued*)

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; 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
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)

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 (performance bias and detection bias) All outcomes	Low risk	Randomisation code was held centrally such that the woman and her healthcare providers were blind to her trial group. Tablets were identical in appearance, weight, colour, taste

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Belizan 1991 (*Continued*)

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 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.
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	1st period (low dose) April 1987 to June 1988 (groups A, B, C); 2nd^{t} 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

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 (performance bias and 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.

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Cong 1995 (*Continued*)

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	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 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-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-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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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CPEP 1997 (*Continued*)

Random sequence generation (selection bias)	Low risk	Packages of study tablets 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 (performance bias and 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

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Crowther 1999 (*Continued*)

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 Intention-to-treat

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 (performance bias and 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	Intention-to-treat 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	1676 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	May 1995 to May 1996, 3 hospital outpatient clinics in Cali, Columbia 1 study group excluded for taking ASA; 2 from control group lost to follow-up

Risk of bias

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Herrera 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	" allocated randomly."
Allocation concealment (selection bias)	Low risk	" allocated randomly."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blind, placebo controlled trial."
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	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	March 2001 to March 2003; 4 outpatient clinics in Bangladesh and Colombia 220 women screened; eco-Doppler ultrasound positive in 53 women; three 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

Risk of bias

Bias	Authors' judgement	Support for judgement

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Herrera 2006 (*Continued*)

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 (performance bias and detection bias) All outcomes	Low 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
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	To our knowledge, maternal BP outcomes have not yet been reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Jarjou 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Random permuted blocks of 4.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	> 20% missing data.
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

Kumar 2009

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Kumar 2009 (*Continued*)

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 (performance bias and 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) All outcomes	Low risk	Attrition < 10%.
Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Unclear 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	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)

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L-Jaramillo 1989 (*Continued*)

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 (performance bias and detection bias) All outcomes	Low risk	Double-blind. Identical containers and tablets prepared by the Faculty of Chemistry and Pharmacy, Central University of Ecuador
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear.
Selective reporting (reporting bias)	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
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	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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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L-Jaramillo 1990 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Authors state that this was a randomised controlled trial 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 (performance bias and detection bias) All outcomes	Unclear risk	Stated double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear.
Selective reporting (reporting bias)	Unclear risk	Not clear.
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	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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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L-Jaramillo 1997 (*Continued*)

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 (performance bias and 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)
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	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 Afiffliated Hospital of Xi'an Medical University Aug 1996 to Dec 1998. No information on consent or ethical approval
Risk of bias	

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Li 2000 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and 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."
Participants	400 pregnant women 20 to 35 years old attending antenatal clinic. Dietary intake about 500 mg calcium and 40 IU vit 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.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not specified.
Allocation concealment (selection bias)	High risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No record of losses to follow-up.

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Marya 1987 (*Continued*)

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 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. 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.

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. Pharmacy dispensed the tablets
Blinding (performance bias and 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.

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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 lost to follow-up (calcium 6, placebo 5)
Participants	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 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.

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 (performance bias and detection bias) All outcomes	Low risk	Double-blind. Containers and tablets prepared by a pharmaceutical firm in Nagpur. Tablets 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 similar; balanced loss to follow-up

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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 tendency for participants to select from a certain part of the pile of envelopes
Participants	500 primiparous Chinese women in 2^{nd} 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 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	July 1992 to Dec 1994.

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 (performance bias and 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	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 vitamins C > 150 mg and/ or E > 75 IU per day; 3) known placental abnormalities; 4) current pregnancy as a result of in vitro fertilization;

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	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 - intrauterine growth restriction, intrauterine fetal death, preterm delivery (before 37 weeks)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants 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 randomised according to a computer-generated random number sequence by an independent third party who had no conflict of interest in the study
Blinding (performance bias and 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.

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S-Ramos 1994

Methods	Double-blind placebo-controlled trial. 4/33 allocated calcium lost to follow-up
Participants	Normotensive nulliparas; positive roll-over test (281/1065) and positive angiotensin II infusion test at 20-24 weeks' gestation (67/281). 67 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

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 (performance bias and detection bias) All outcomes	Low risk	Double-blind. Tablets prepared by 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. Intention-to-treat 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

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		still have significantly favoured the calcium group

Taherian 2002

Methods	"Healthy antepartum cases were randomized and divided into 3 groups."
Participants	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 and those with known hazardous condition (multifetal gestation, hydatidiform mole)
Interventions	Group 1 received 75 mg aspirin each day from 20^{th} 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

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 (performance bias and detection bias) All outcomes	High risk	No placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No record of losses to follow-up.

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Taherian 2002 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No information.
Other bias	High risk	High - limited information on methods. No mention of loss to follow-up.

Villar 1987

Methods	Double-blind, randomised controlled trial.
Participants	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 John 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	Recruitment 1983-1985. 34 black women from John Hopkins Hospital, Baltimore, USA, 18 white women from Rosario, Argentina

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 (performance bias and detection bias) All outcomes	Low risk	Tablets same weight, size and colour, prepared by The John 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 John Hopkins Hospital only also received vitamin preparations containing 200 mg calcium/day

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Villar 1990

Methods	Double-blind, randomised trial.
Participants	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	John Hopkins Hospital, Baltimore, 1985-1988.

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 coordinator responsible for assigning treatment. Identical tablets and containers prepared at The John Hopkins Hospital pharmacy
Blinding (performance bias and 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

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WHO 2006 (*Continued*)

Participants	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 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).

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. Placebo and calcium tablets identical
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind.

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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	Intention-to-treat principle. Baseline characteristics, compliance and drop-out rates similar

ASA: acetylsalicylic acid
BMI: body mass index
BP: blood pressure
DBP: diastolic blood pressure
dl: decilitre
ICU: intensive care unit
IU: international units
mcg: microgram
mg: milligram
NICU: neonatal intensive care unit
PE: pulmonary embolism
PI: pulsatility index
PIH: pregnancy-induced hypertension
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
August 2002	Excluded pending full report of results. Inadequate data in abstracts for inclusion
Belizan 1983	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.

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(*Continued*)

	Study design: randomised, no further information.
Boggess 1997	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 to 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 found in blood lead levels between women receiving calcium 1000 mg daily from 13-19 weeks (n = 24) or placebo (n = 26)
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). Biochemical outcomes only. Abstract only
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. No outcomes specified for this review were reported
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
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 no clinically relevant outcomes reported, 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

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Lavin 1986	Planned trial of calcium versus placebo in women with a positive roll-over test at 28-32 weeks. Trial apparently cancelled
MacDonald 1986	RCT of calcium AND vitamin D versus placebo in 55 Asian women with no method or results provided in this personal communication from 1986. Attempts to contact the author for more details were unsuccessful
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".
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 blood pressure 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. Biochemical data on only 87 women
Repke 1989	N = 255. Presented as abstract only. No clinical data available Interventions: calcium 2 g/day vs placebo, after 20 weeks of pregnancy. Study design: 'randomised clinical trial'.
S-Ramos 1995	N = 75. Excluded because calcium 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), versus 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)
Suzuki 1996	N = 152. Not a randomised trial. 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

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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

ASA: acetylsalicylic acid
BP: blood pressure
DBP: diastolic blood pressure
RCT: randomised controlled trial
vs: versus

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

Asemi 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Diogenes 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Goldberg 2013

Methods	
Participants	
Interventions	

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Goldberg 2013 (*Continued*)

Outcomes	
Notes	

Herrera 2006a

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Jarjou 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Sulovic 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Zheng 2000

Methods	
Participants	
Interventions	

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Zheng 2000 (*Continued*)

Outcomes	
Notes	Awaiting translation.

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

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.

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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 [0.65, 0.97]
6.1 Low calcium diet	4	9732	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.97]
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]
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]

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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 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]
16.2 Low calcium diet	3	9026	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.21]
17 Childhood systolic blood pressure > 95th percentile	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 Childhood diastolic blood pressure > 95th percentile	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 Childhood dental caries	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]

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]

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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]
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]

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

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]

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1.5 Dietary calcium not specified	1	30	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.02]

Comparison 5. Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

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]

Comparison 6. Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

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 Preterm birth	4	1190	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.87]
2.1 Calcium supplementation alone	1	422	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.75]
2.2 Calcium plus vitamin D	1	660	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.00, 2.41]
2.3 Calcium plus linoleic acid	1	48	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.15]
2.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.23]
3 Neonatal intensive care unit admission	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.20, 0.99]
3.1 Calcium supplementation alone	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.20, 0.99]
3.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Calcium plus linoleic acid	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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4 Stillbirth or death before discharge	5	1025	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.14, 1.67]
4.1 Calcium supplementation alone	1	171	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.07, 16.29]
4.2 Calcium plus vitamin D	1	660	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.15]
4.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.08, 4.41]
4.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.39]
5 Placental abruption	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Caesarean section	4	521	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.15]
6.1 Calcium supplementation alone	2	387	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.40, 2.22]
6.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.35, 0.87]
7 Severe pre-eclampsia	2	146	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.21]
7.1 Calcium supplementation alone	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Calcium plus vitamin D	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Calcium plus linoleic acid	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.56]
7.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.04, 3.23]
8 Pre-eclampsia	9	2234	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.28, 0.52]
8.1 Calcium supplementation alone	4	980	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.57]
8.2 Calcium plus vitamin D	2	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.31, 0.78]
8.3 Calcium plus linoleic acid	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.09, 0.60]
8.4 Calcium plus antioxidants	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.01]
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 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]
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]

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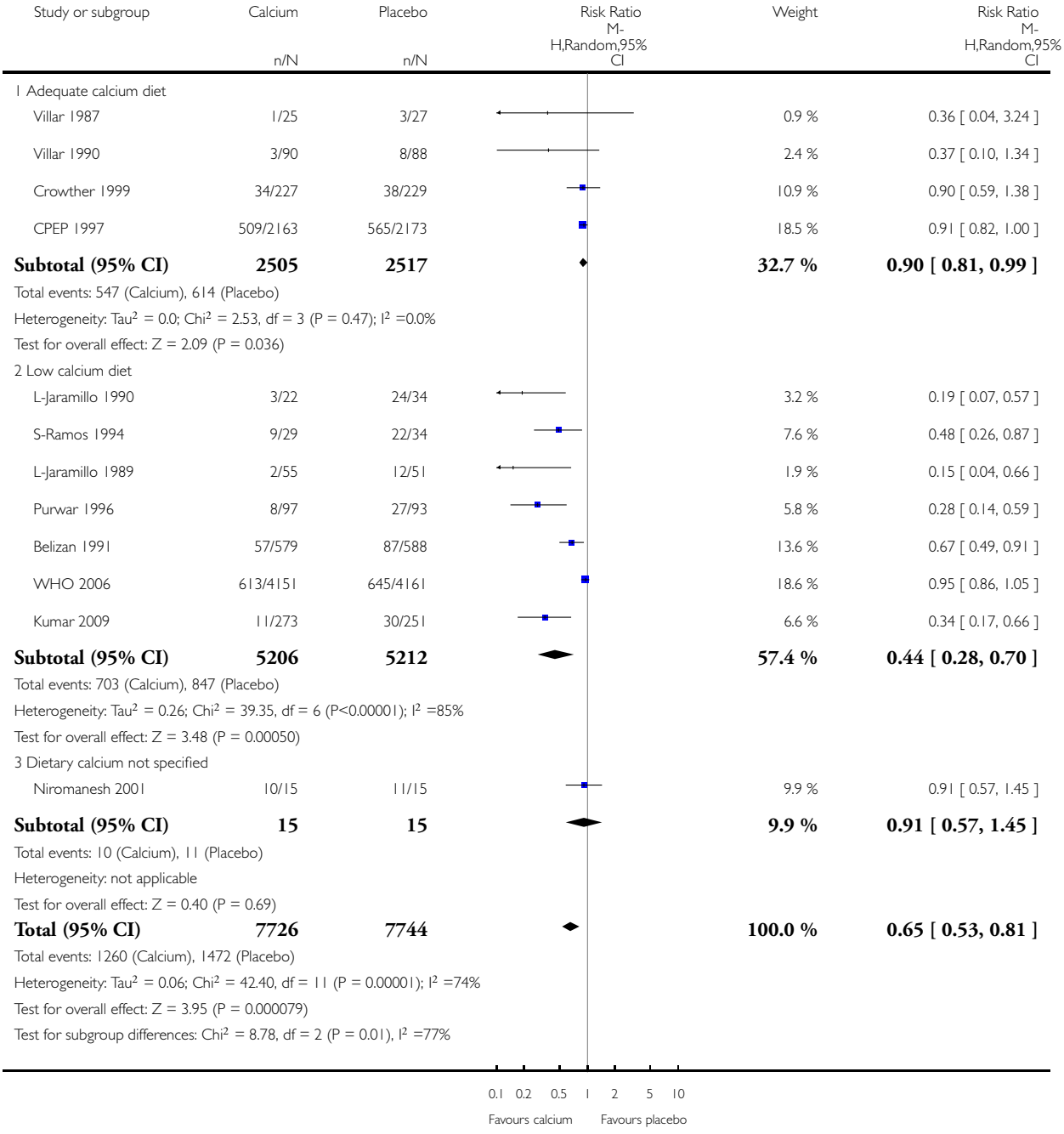
Analysis 1.1. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 1 High blood pressure (with or without proteinuria).

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

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

Outcome: 1 High blood pressure (with or without proteinuria)



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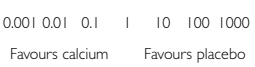
Analysis 1.2. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 2 Pre-eclampsia.

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

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 Adequate calcium diet					
Villar 1987	1/25	3/27		2.4 %	0.36 [0.04, 3.24]
Villar 1990	0/90	3/88		1.4 %	0.14 [0.01, 2.67]
Crowther 1999	10/227	23/229		10.6 %	0.44 [0.21, 0.90]
CPEP 1997	158/2163	168/2173		16.9 %	0.94 [0.77, 1.16]
Subtotal (95% CI)	**2505**	**2517**		**31.3 %**	**0.62 [0.32, 1.20]**
Total events: 169 (Calcium), 197 (Placebo)					
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 6.20$, df = 3 (P = 0.10); $I^2 = 52\%$					
Test for overall effect: Z = 1.43 (P = 0.15)					
2 Low calcium diet					
L-Jaramillo 1990	0/22	8/34		1.6 %	0.09 [0.01, 1.48]
S-Ramos 1994	4/29	15/34		7.8 %	0.31 [0.12, 0.84]
L-Jaramillo 1989	2/55	12/51		4.7 %	0.15 [0.04, 0.66]
Purwar 1996	2/97	11/93		4.6 %	0.17 [0.04, 0.77]
L-Jaramillo 1997	4/125	21/135		7.3 %	0.21 [0.07, 0.58]
Belizan 1991	15/579	23/588		11.6 %	0.66 [0.35, 1.26]
WHO 2006	171/4151	186/4161		17.0 %	0.92 [0.75, 1.13]
Kumar 2009	11/273	30/251		11.2 %	0.34 [0.17, 0.66]
Subtotal (95% CI)	**5331**	**5347**		**65.7 %**	**0.36 [0.20, 0.65]**
Total events: 209 (Calcium), 306 (Placebo)					
Heterogeneity: $Tau^2 = 0.44$; $Chi^2 = 29.35$, df = 7 (P = 0.00012); $I^2 = 76\%$					
Test for overall effect: Z = 3.40 (P = 0.00067)					
3 Dietary calcium not specified					
Niromanesh 2001	1/15	7/15		2.9 %	0.14 [0.02, 1.02]
Subtotal (95% CI)	**15**	**15**		**2.9 %**	**0.14 [0.02, 1.02]**



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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: 1 (Calcium), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.053)					
Total (95% CI)	**7851**	**7879**	◆	**100.0 %**	**0.45 [0.31, 0.65]**
Total events: 379 (Calcium), 510 (Placebo)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 40.31, df = 12 (P = 0.00006); I^2 =70%					
Test for overall effect: Z = 4.29 (P = 0.000018)					
Test for subgroup differences: Chi^2 = 2.73, df = 2 (P = 0.26), I^2 =27%					

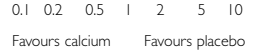
Analysis 1.3. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 3 Preterm birth.

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

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 Adequate calcium diet					
Villar 1987	0/25	0/27			Not estimable
Villar 1990	7/94	20/95	■	6.6 %	0.35 [0.16, 0.80]
Crowther 1999	10/227	23/229	■	7.9 %	0.44 [0.21, 0.90]
CPEP 1997	248/2163	229/2173	■	25.5 %	1.09 [0.92, 1.29]
Subtotal (95% CI)	**2509**	**2524**	◆	**39.9 %**	**0.59 [0.26, 1.33]**
Total events: 265 (Calcium), 272 (Placebo)					
Heterogeneity: Tau^2 = 0.42; Chi^2 = 12.31, df = 2 (P = 0.002); I^2 =84%					
Test for overall effect: Z = 1.26 (P = 0.21)					
2 Low calcium diet					
L-Jaramillo 1990	0/22	4/34	←	0.7 %	0.17 [0.01, 2.99]



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Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
S-Ramos 1994	5/29	8/34		4.7 %	0.73 [0.27, 1.99]
Purwar 1996	2/97	6/93		2.1 %	0.32 [0.07, 1.54]
L-Jaramillo 1997	0/125	0/135			Not estimable
Belizan 1991	33/527	37/542		14.1 %	0.92 [0.58, 1.44]
WHO 2006	398/4038	436/4042		27.0 %	0.91 [0.80, 1.04]
Kumar 2009	19/273	32/251		11.6 %	0.55 [0.32, 0.94]
Subtotal (95% CI)	**5111**	**5131**		**60.1 %**	**0.81 [0.64, 1.02]**
Total events: 457 (Calcium), 523 (Placebo)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.34, df = 5 (P = 0.27); I^2 =21%					
Test for overall effect: Z = 1.76 (P = 0.078)					
Total (95% CI)	**7620**	**7655**		**100.0 %**	**0.76 [0.60, 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%					
Test for overall effect: Z = 2.23 (P = 0.026)					
Test for subgroup differences: Chi^2 = 0.53, df = 1 (P = 0.47), I^2 =0.0%					

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

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

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 Adequate calcium diet					
CPEP 1997	343/2163	315/2173		62.2 %	1.09 [0.95, 1.26]
Subtotal (95% CI)	**2163**	**2173**		**62.2 %**	**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)					
2 Low calcium diet					
S-Ramos 1994	1/29	4/34		0.7 %	0.29 [0.03, 2.48]
Belizan 1991	72/544	65/554		12.7 %	1.13 [0.82, 1.54]
WHO 2006	114/3953	123/3956		24.3 %	0.93 [0.72, 1.19]
Subtotal (95% CI)	**4526**	**4544**		**37.8 %**	**0.98 [0.81, 1.19]**
Total events: 187 (Calcium), 192 (Placebo)					
Heterogeneity: Chi^2 = 2.18, df = 2 (P = 0.34); I^2 =8%					
Test for overall effect: Z = 0.17 (P = 0.86)					
Total (95% CI)	**6689**	**6717**		**100.0 %**	**1.05 [0.94, 1.18]**
Total events: 530 (Calcium), 507 (Placebo)					
Heterogeneity: Chi^2 = 2.83, df = 3 (P = 0.42); I^2 =0.0%					
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 =0.0%					

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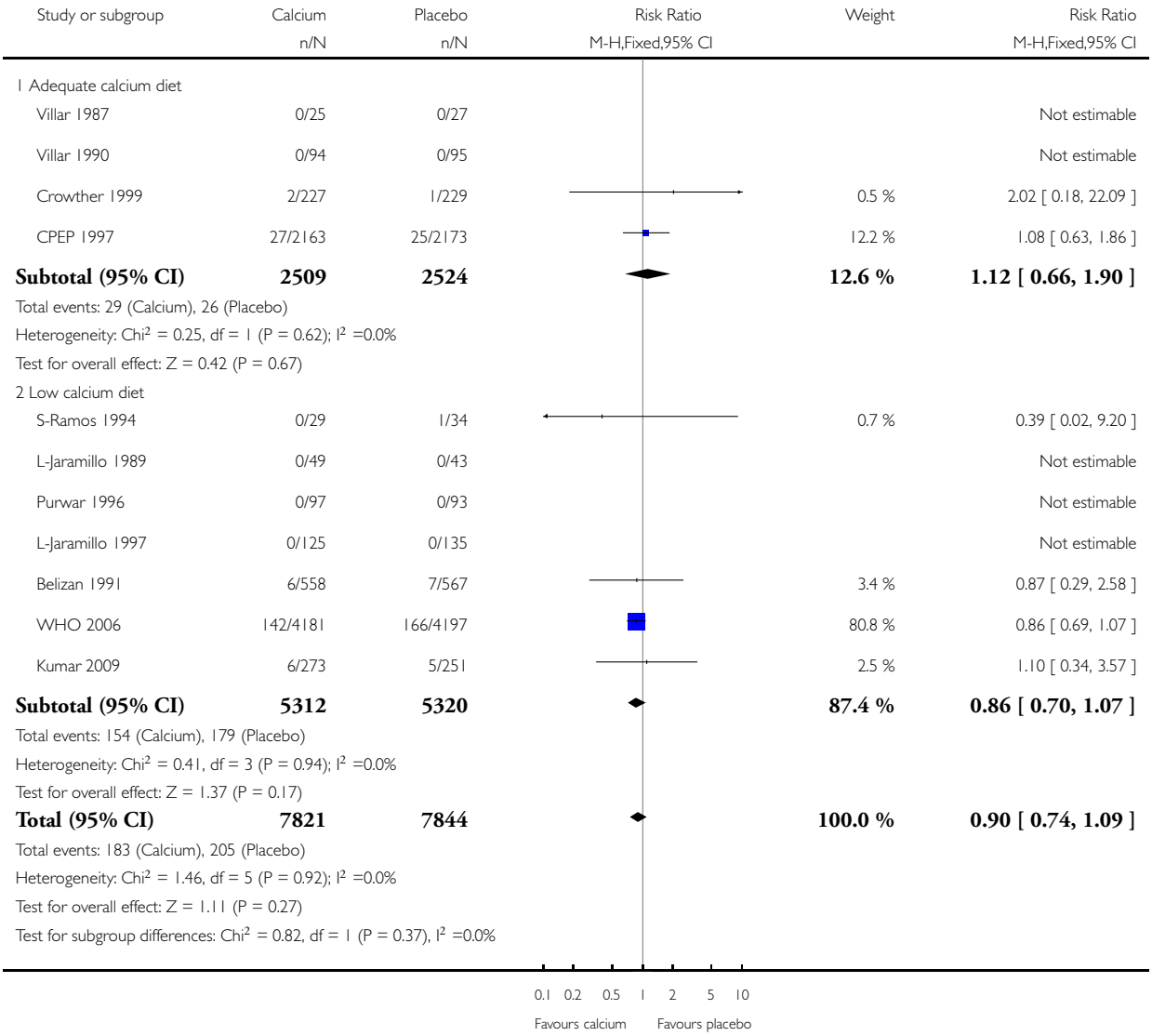
Analysis 1.5. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 5 Stillbirth or death before discharge from hospital.

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

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

Outcome: 5 Stillbirth or death before discharge from hospital



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

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

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 Low calcium diet					
S-Ramos 1994	0/29	1/34		0.7 %	0.39 [0.02, 9.20]
Purwar 1996	0/97	0/93			Not estimable
Belizan 1991	0/579	0/588			Not estimable
WHO 2006	167/4151	209/4161		99.3 %	0.80 [0.66, 0.98]
Subtotal (95% CI)	**4856**	**4876**		**100.0 %**	**0.80 [0.65, 0.97]**
Total events: 167 (Calcium), 210 (Placebo)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.23 (P = 0.026)					
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 %**	**0.80 [0.65, 0.97]**
Total events: 167 (Calcium), 210 (Placebo)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.23 (P = 0.026)					
Test for subgroup differences: Not applicable					

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

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

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 Adequate calcium diet					
Villar 1987	0/25	0/27			Not estimable
Villar 1990	0/94	0/95			Not estimable
CPEP 1997	13/2295	16/2294		38.1 %	0.81 [0.39, 1.68]
Subtotal (95% CI)	**2414**	**2416**		**38.1 %**	**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)					
2 Low calcium diet					
WHO 2006	17/4151	22/4161		52.4 %	0.77 [0.41, 1.46]
Belizan 1991	6/593	4/601		9.5 %	1.52 [0.43, 5.36]
Subtotal (95% CI)	**4744**	**4762**		**61.9 %**	**0.89 [0.51, 1.55]**
Total events: 23 (Calcium), 26 (Placebo)					
Heterogeneity: Chi^2 = 0.88, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
Total (95% CI)	**7158**	**7178**		**100.0 %**	**0.86 [0.55, 1.34]**
Total events: 36 (Calcium), 42 (Placebo)					
Heterogeneity: Chi^2 = 0.91, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.67 (P = 0.50)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.85), I^2 =0.0%					

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

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

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 Adequate calcium diet					
Villar 1990	16/94	17/95		1.2 %	0.95 [0.51, 1.77]
Crowther 1999	46/227	46/229		3.2 %	1.01 [0.70, 1.45]
CPEP 1997	366/2163	390/2173		27.6 %	0.94 [0.83, 1.07]
Subtotal (95% CI)	**2484**	**2497**		**32.0 %**	**0.95 [0.84, 1.07]**
Total events: 428 (Calcium), 453 (Placebo)					
Heterogeneity: Chi^2 = 0.12, df = 2 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.84 (P = 0.40)					
2 Low calcium diet					
S-Ramos 1994	1/29	6/34		0.4 %	0.20 [0.02, 1.53]
Purwar 1996	6/97	7/93		0.5 %	0.82 [0.29, 2.35]
Belizan 1991	60/544	66/554		4.6 %	0.93 [0.67, 1.29]
WHO 2006	809/4181	854/4197		60.4 %	0.95 [0.87, 1.04]
Kumar 2009	41/273	27/251		2.0 %	1.40 [0.89, 2.20]
Subtotal (95% CI)	**5124**	**5129**		**68.0 %**	**0.96 [0.88, 1.04]**
Total events: 917 (Calcium), 960 (Placebo)					
Heterogeneity: Chi^2 = 5.08, df = 4 (P = 0.28); I^2 =21%					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	**7608**	**7626**		**100.0 %**	**0.95 [0.89, 1.02]**
Total events: 1345 (Calcium), 1413 (Placebo)					
Heterogeneity: Chi^2 = 5.21, df = 7 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 1.35 (P = 0.18)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%					

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

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

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 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					
2 Low calcium diet					
WHO 2006	201/4151	194/4161		100.0 %	1.04 [0.86, 1.26]
Subtotal (95% CI)	**4151**	**4161**		**100.0 %**	**1.04 [0.86, 1.26]**
Total events: 201 (Calcium), 194 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					
Total (95% CI)	**4151**	**4161**		**100.0 %**	**1.04 [0.86, 1.26]**
Total events: 201 (Calcium), 194 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					
Test for subgroup differences: Not applicable					

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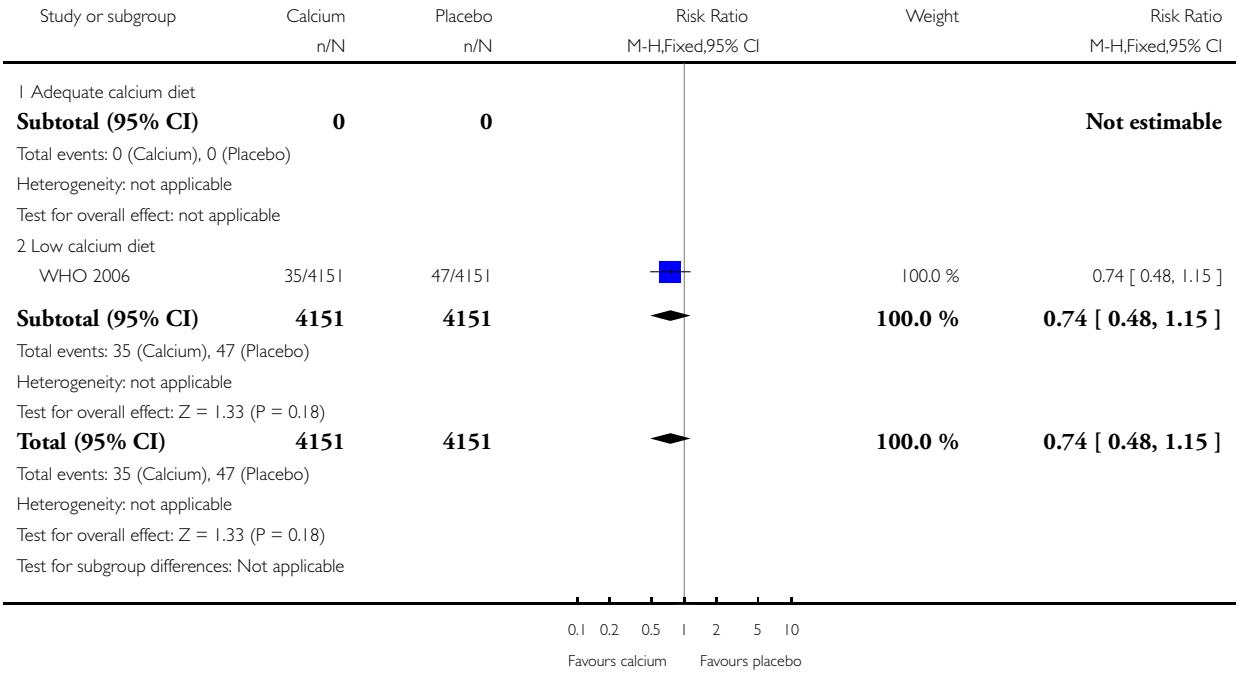
Analysis 1.10. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 10 Severe pre-eclampsia.

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

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

Outcome: 10 Severe pre-eclampsia



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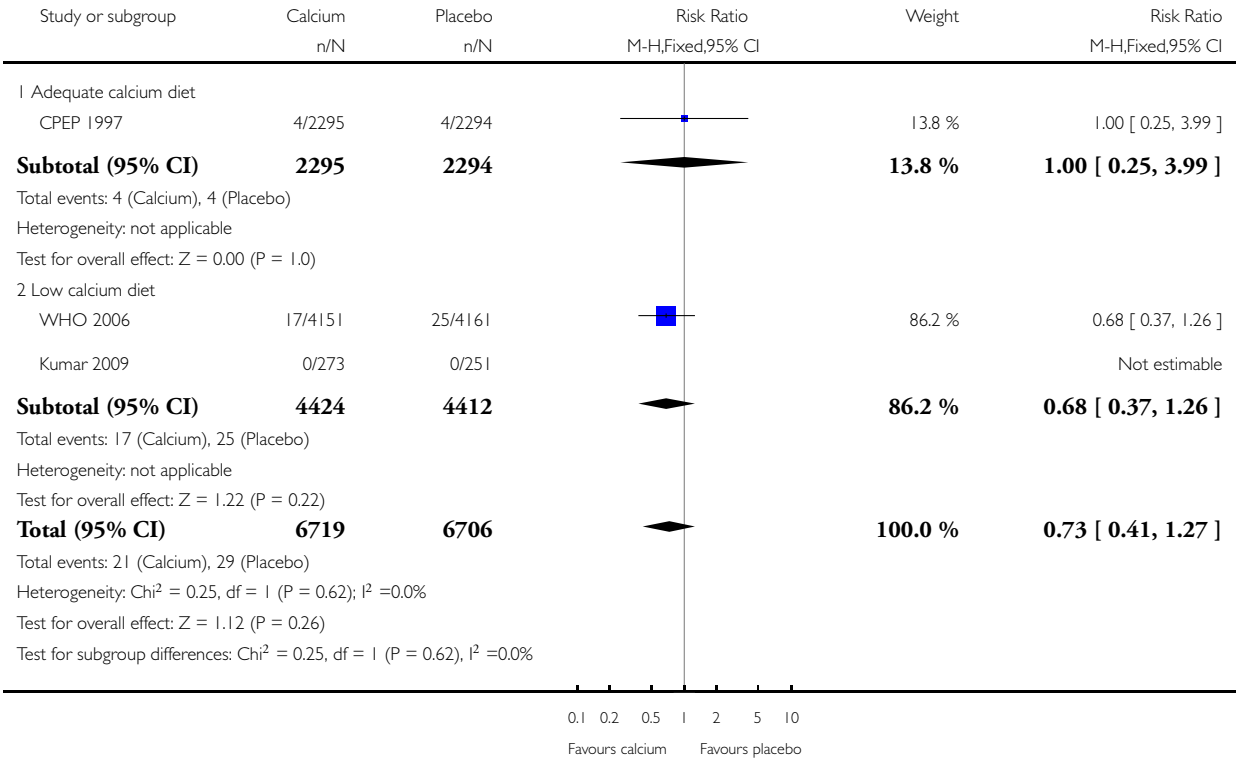
Analysis 1.11. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 11 Eclampsia.

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

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

Outcome: 11 Eclampsia



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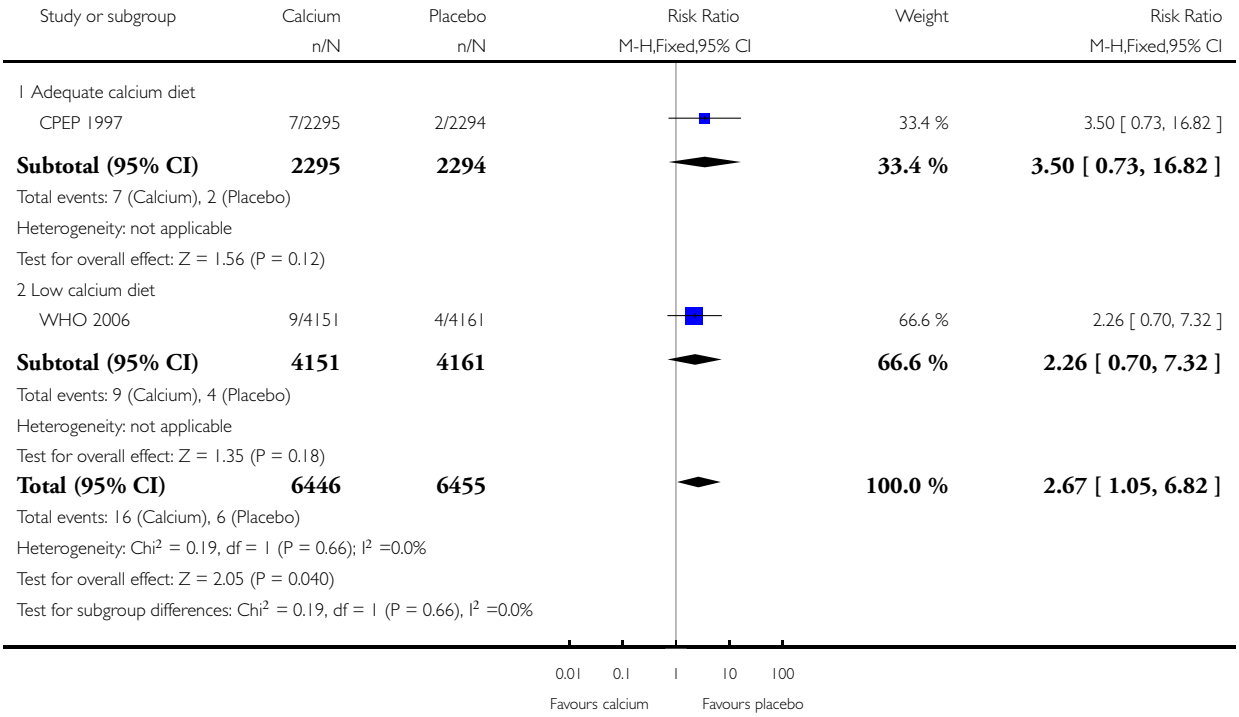
Analysis 1.12. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 12 HELLP syndrome.

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

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

Outcome: 12 HELLP syndrome



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

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

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 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					
2 Low calcium diet					
WHO 2006	116/4151	138/4161		100.0 %	0.84 [0.66, 1.07]
Subtotal (95% CI)	**4151**	**4161**		**100.0 %**	**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 %**	**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					

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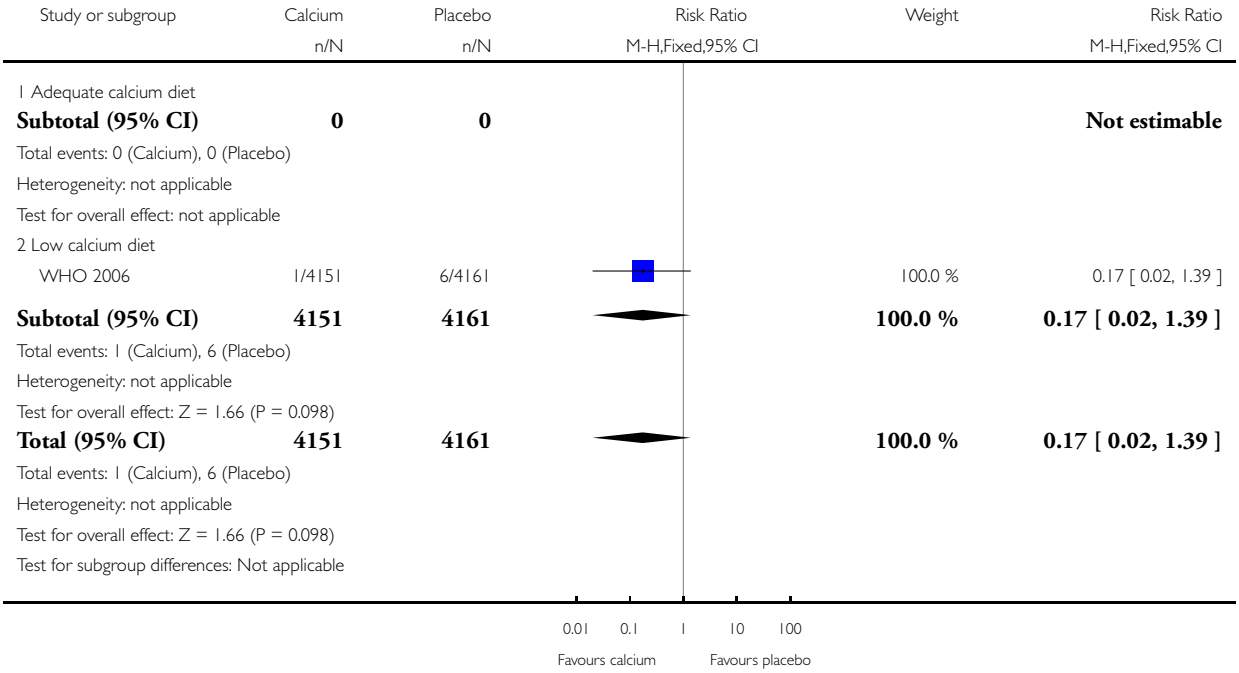
Analysis 1.14. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 14 Maternal death.

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

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

Outcome: 14 Maternal death



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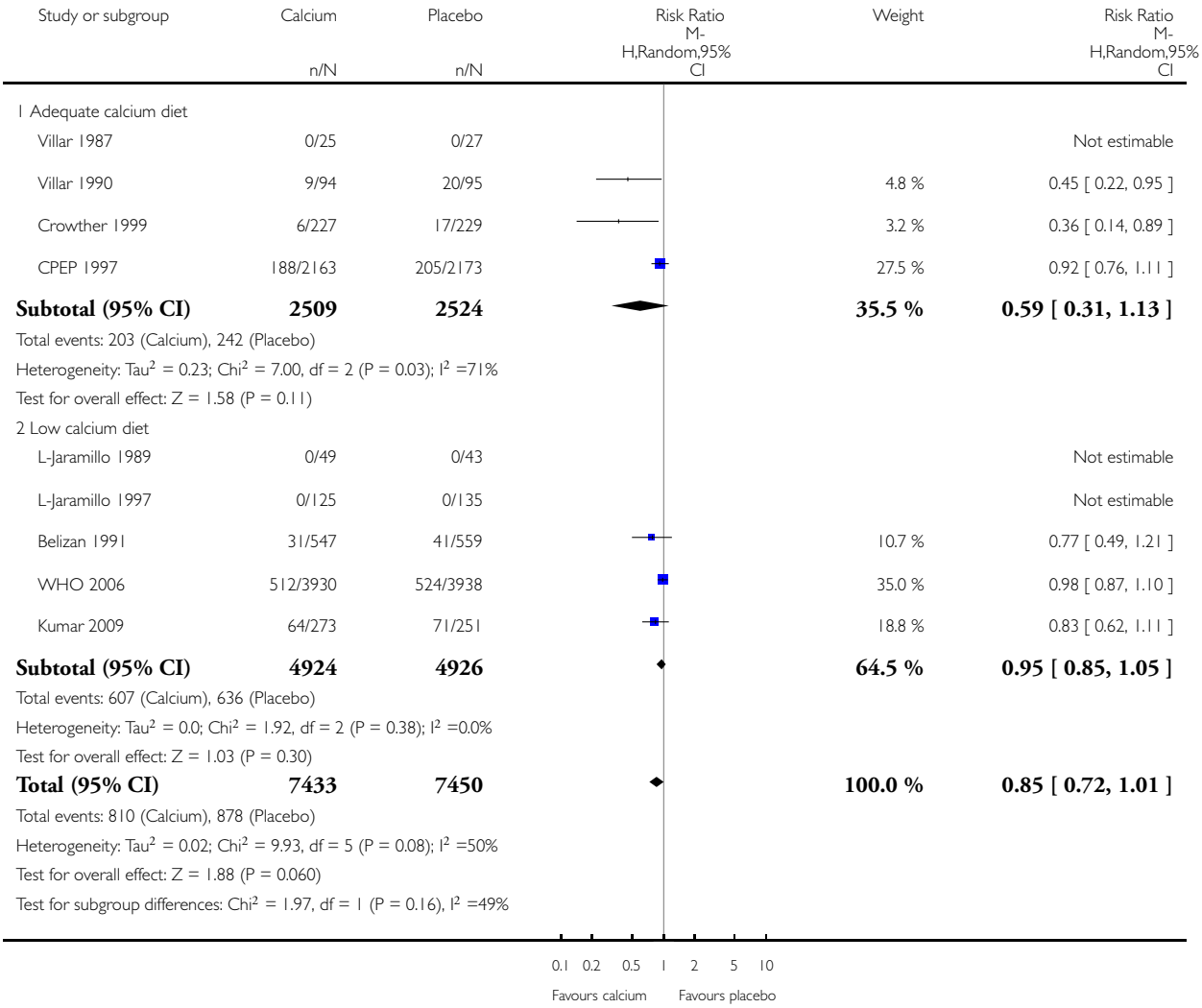
Analysis 1.15. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 15 Birthweight < 2500 g.

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

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

Outcome: 15 Birthweight < 2500 g



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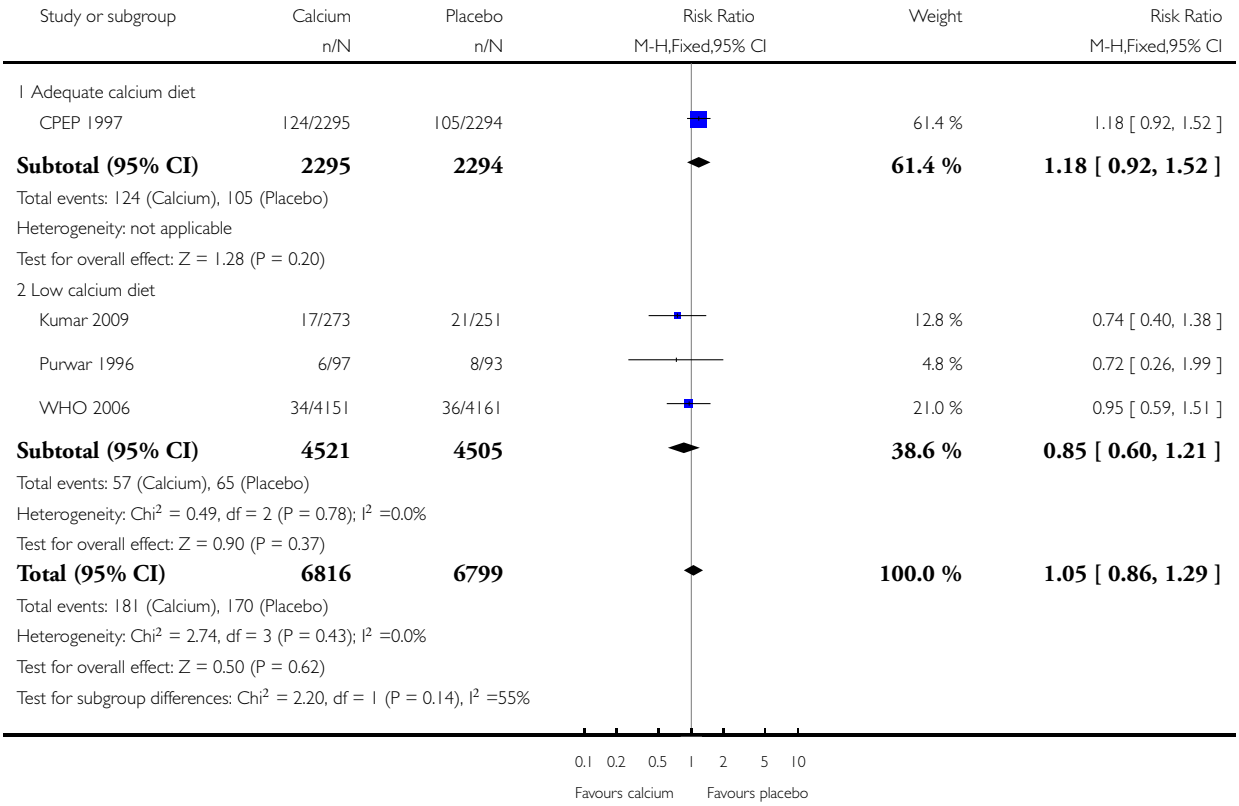
Analysis 1.16. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 16 Neonate small-for-gestational age as defined by trial authors.

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

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



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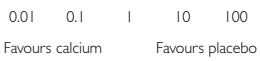
Analysis 1.17. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 17 Childhood systolic blood pressure > 95th percentile.

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

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

Outcome: 17 Childhood systolic blood pressure > 95th percentile

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 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					
2 Low calcium diet					
Belizan 1991	29/254	50/260		100.0 %	0.59 [0.39, 0.91]
Subtotal (95% CI)	**254**	**260**		**100.0 %**	**0.59 [0.39, 0.91]**
Total events: 29 (Calcium), 50 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
Total (95% CI)	**254**	**260**		**100.0 %**	**0.59 [0.39, 0.91]**
Total events: 29 (Calcium), 50 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
Test for subgroup differences: Not applicable					



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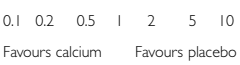
Analysis 1.18. Comparison 1 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium, Outcome 18 Childhood diastolic blood pressure > 95th percentile.

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

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

Outcome: 18 Childhood diastolic blood pressure > 95th percentile

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 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					
2 Low calcium diet					
Belizan 1991	26/254	33/260		100.0 %	0.81 [0.50, 1.31]
Subtotal (95% CI)	**254**	**260**		**100.0 %**	**0.81 [0.50, 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 %**	**0.81 [0.50, 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					



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

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

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

Outcome: 19 Childhood dental caries

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 Low calcium diet					
Belizan 1991	62/98	84/97		100.0 %	0.73 [0.62, 0.87]
Total (95% CI)	**98**	**97**		**100.0 %**	**0.73 [0.62, 0.87]**
Total events: 62 (Calcium), 84 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.62 (P = 0.00029)					
Test for subgroup differences: Not applicable					

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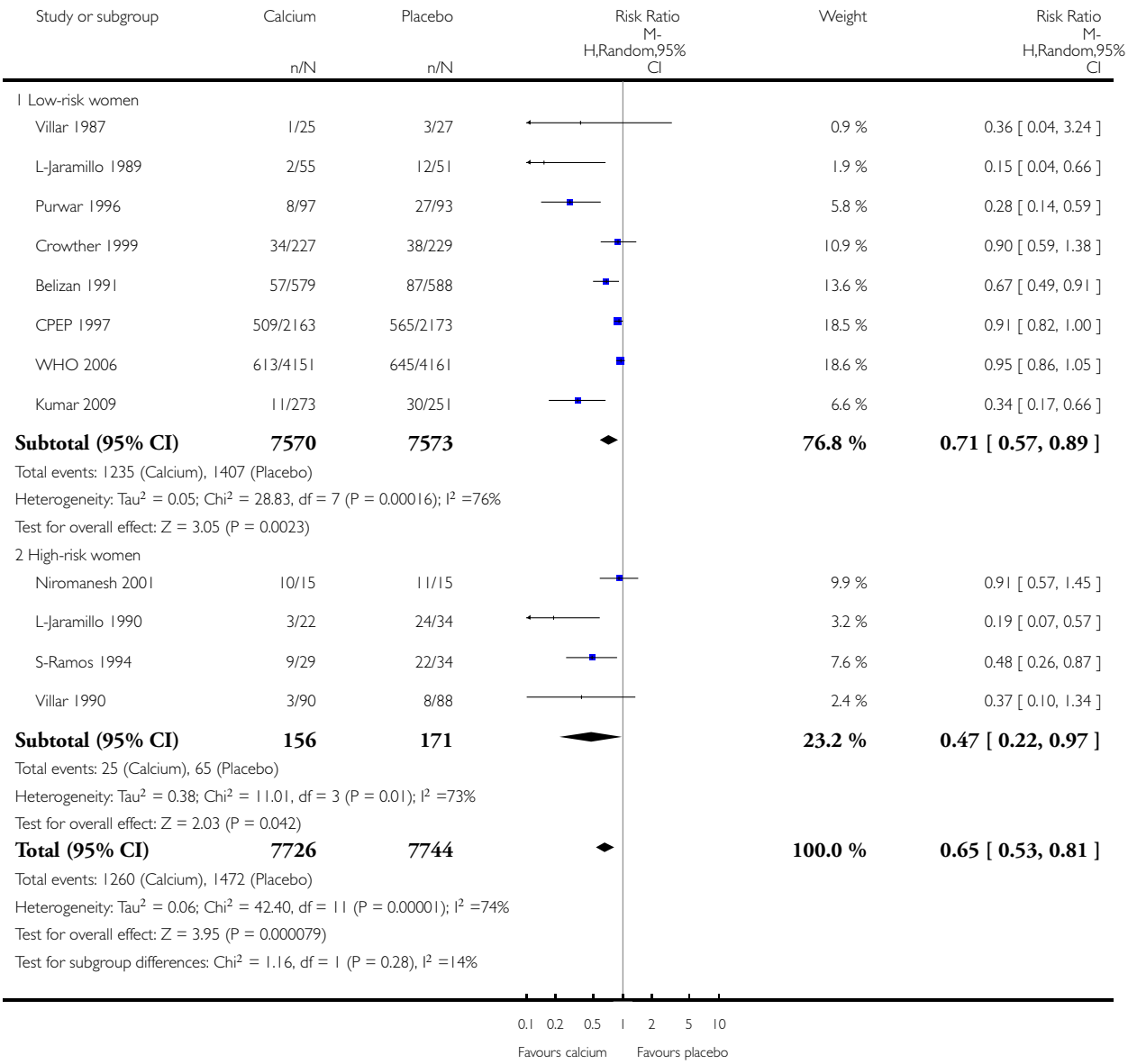
Analysis 2.1. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 1 High blood pressure (with or without proteinuria).

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

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

Outcome: 1 High blood pressure (with or without proteinuria)



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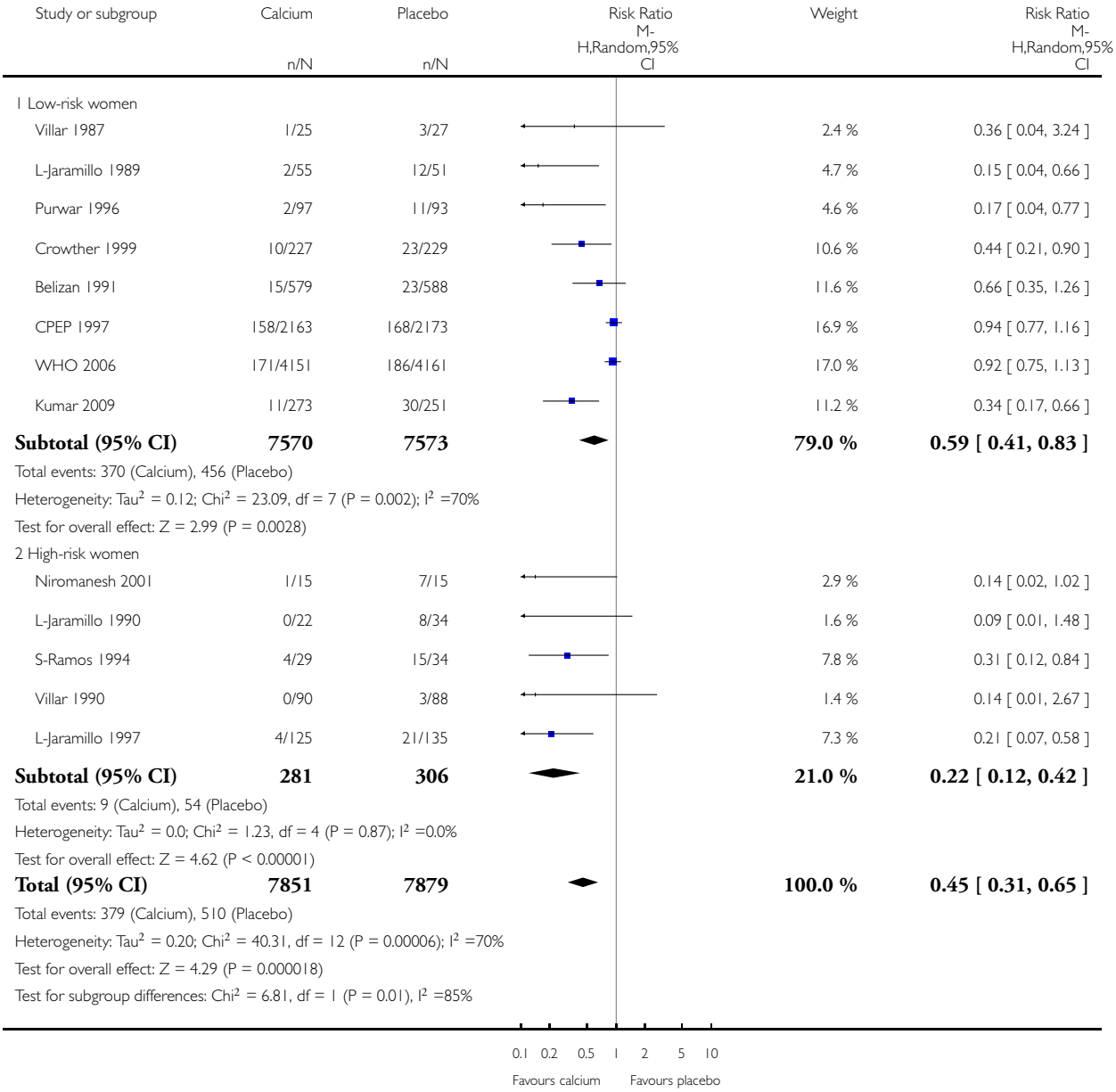
Analysis 2.2. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 2 Pre-eclampsia.

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

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

Outcome: 2 Pre-eclampsia



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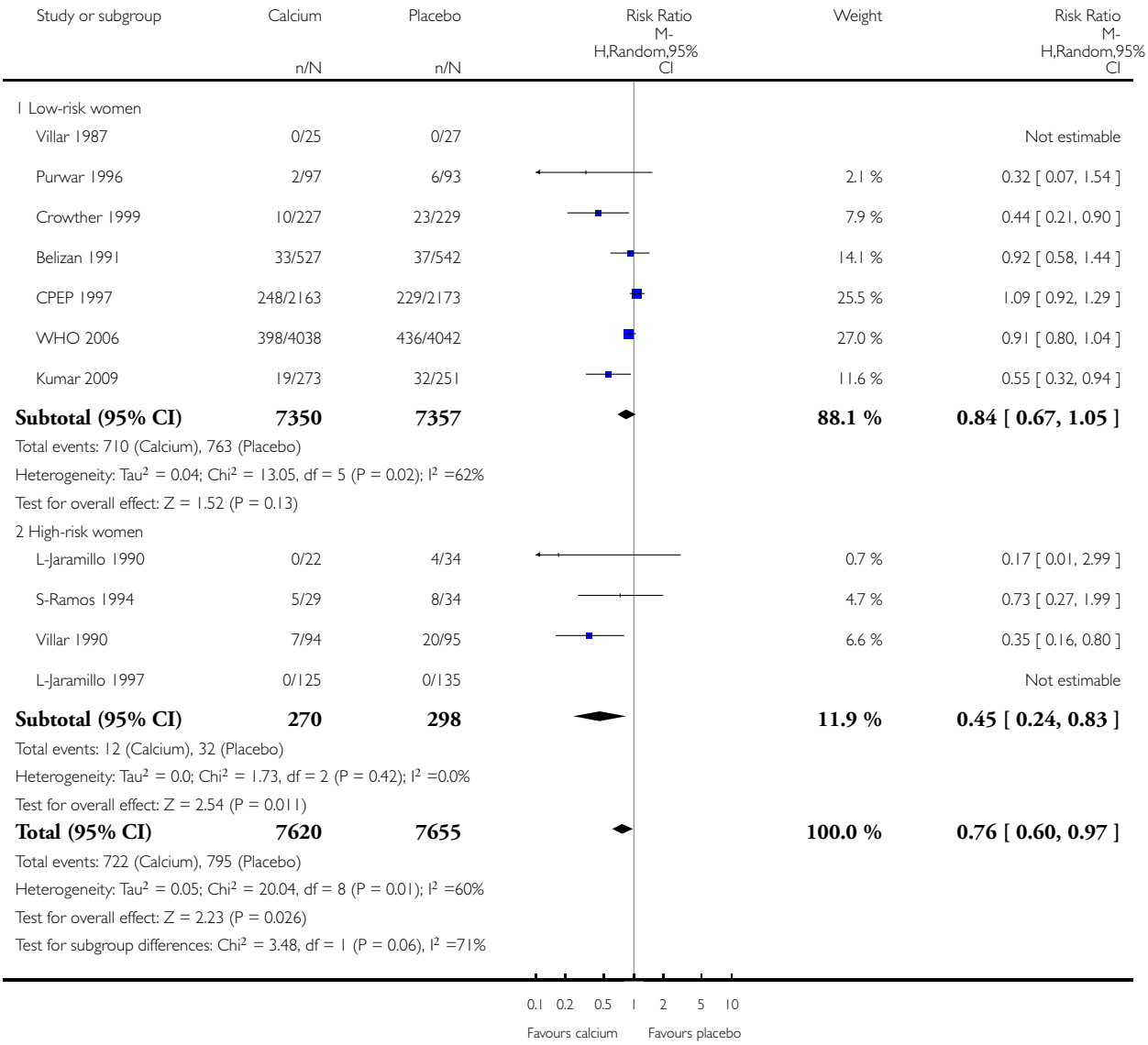
Analysis 2.3. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 3 Preterm birth.

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

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

Outcome: 3 Preterm birth



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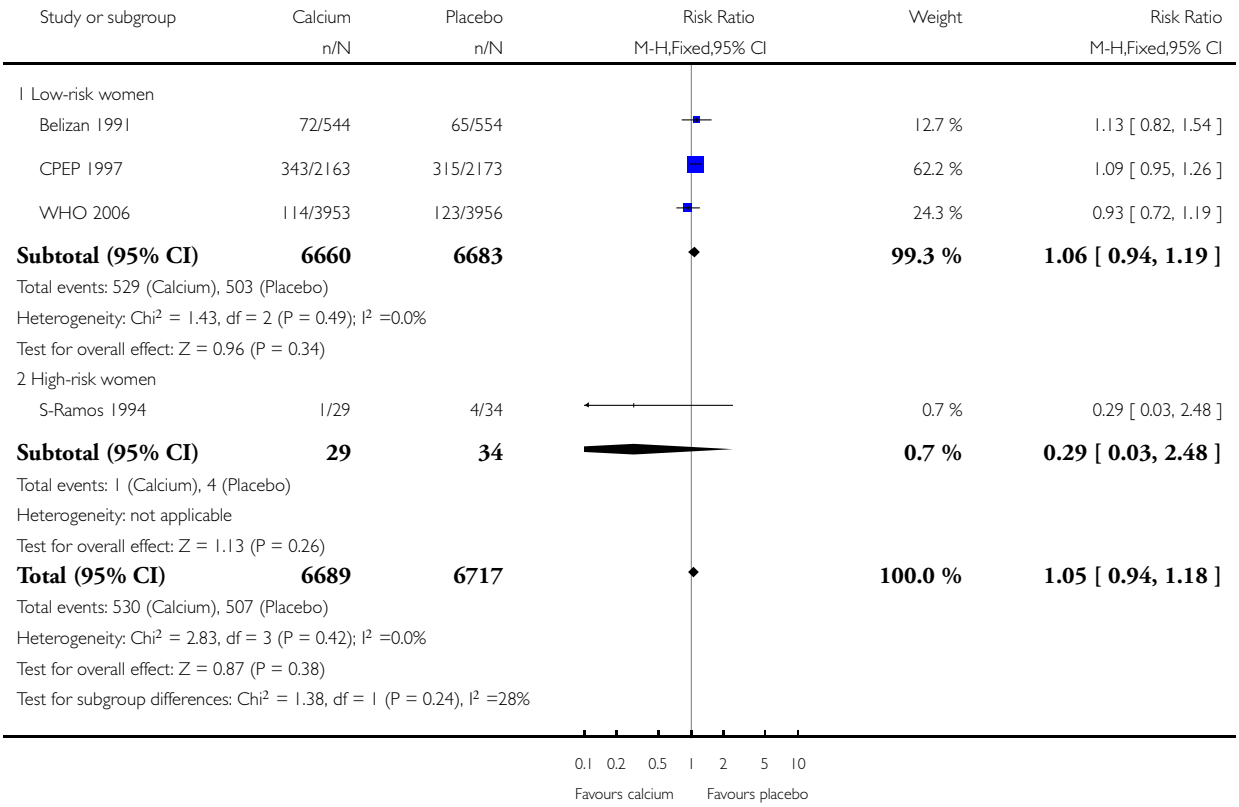
Analysis 2.4. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 4 Admission to neonatal intensive care unit.

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

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

Outcome: 4 Admission to neonatal intensive care unit



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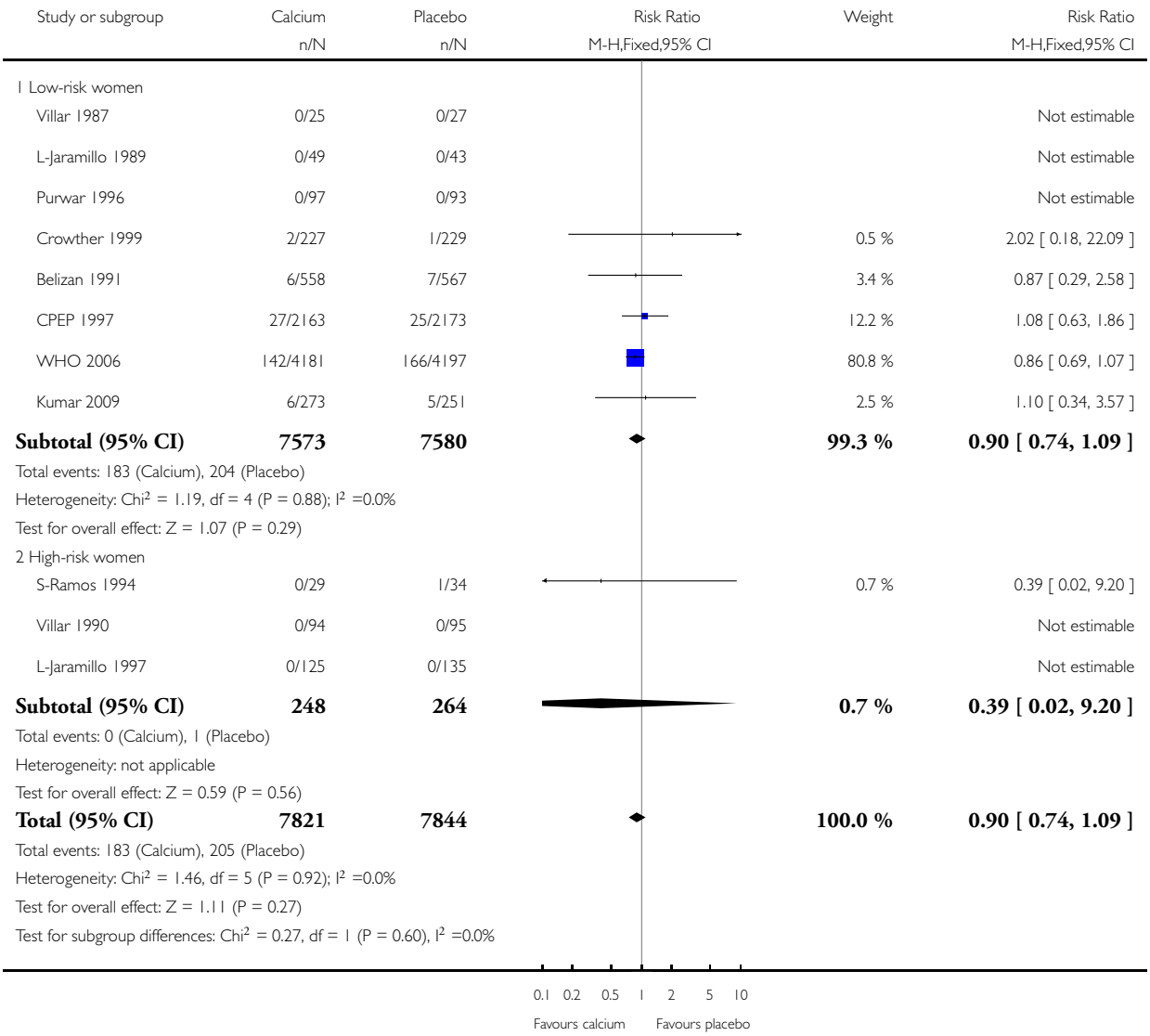
Analysis 2.5. Comparison 2 Routine high-dose calcium supplementation in pregnancy by hypertension risk, Outcome 5 Stillbirth or death before discharge from hospital.

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

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

Outcome: 5 Stillbirth or death before discharge from hospital



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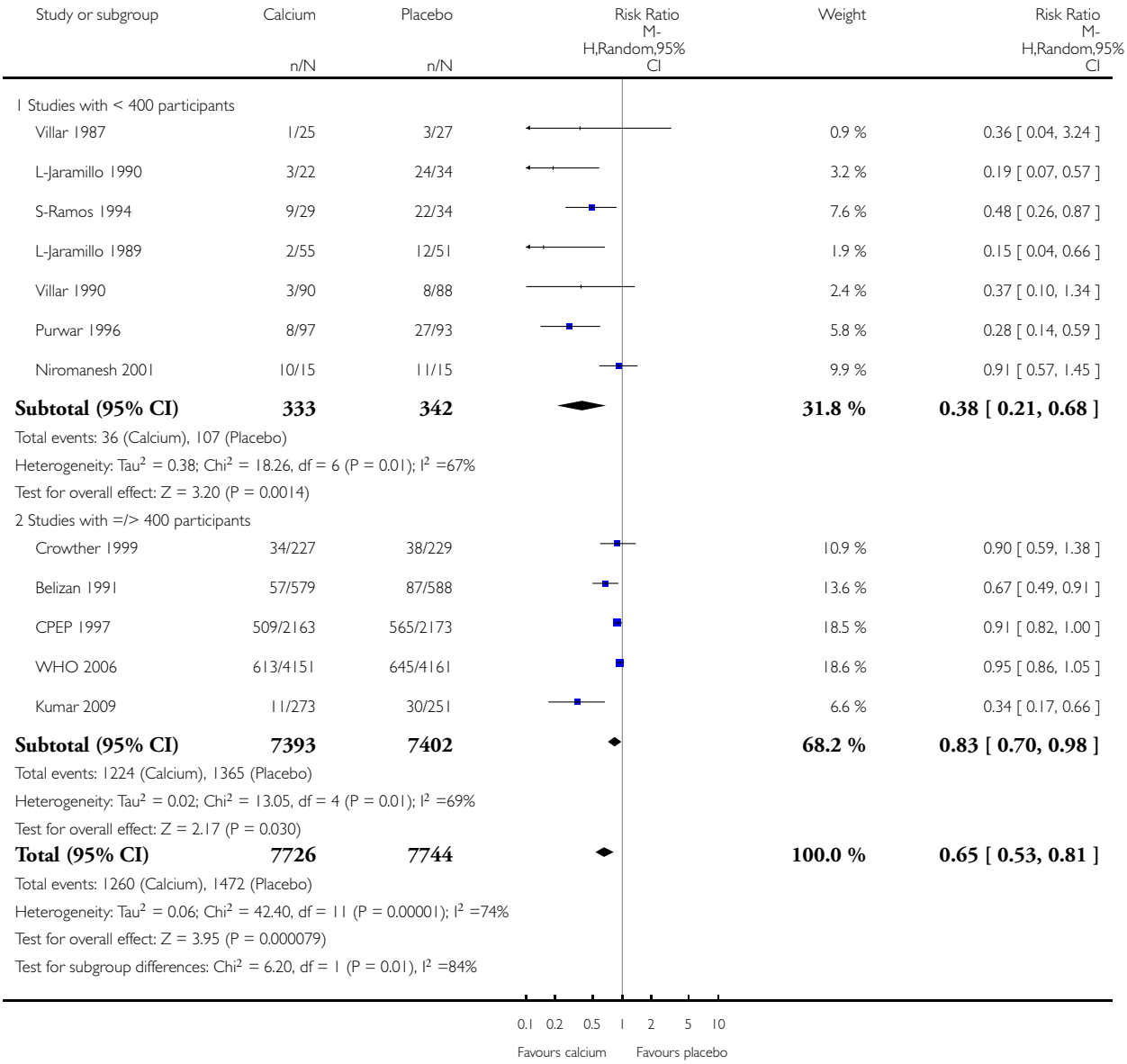
Analysis 3.1. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 1 High blood pressure (with or without proteinuria).

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

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

Outcome: 1 High blood pressure (with or without proteinuria)



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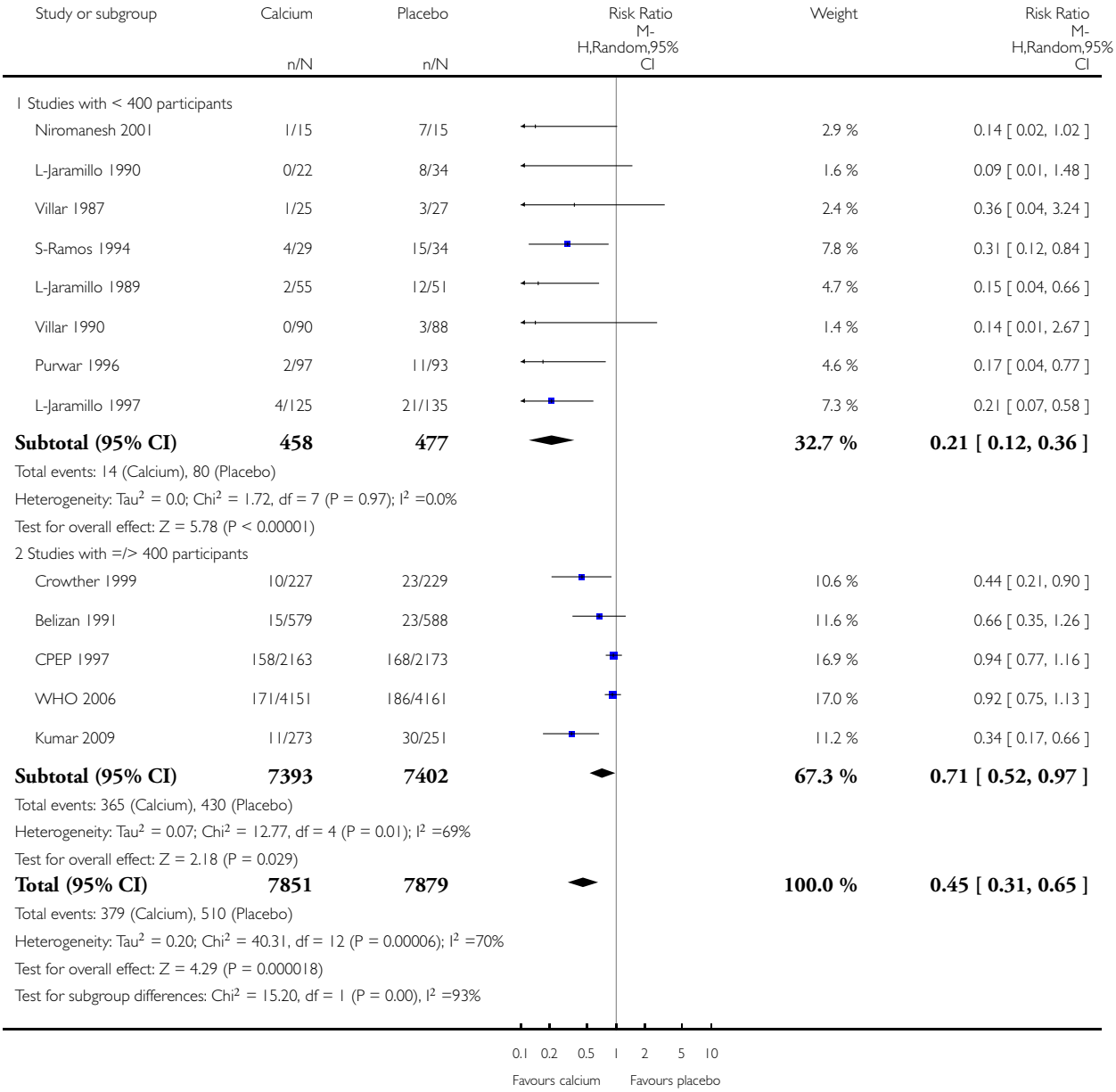
Analysis 3.2. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 2 Pre-eclampsia.

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

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

Outcome: 2 Pre-eclampsia



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

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

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
1 Studies with < 400 participants					
Villar 1987	0/25	0/27			Not estimable
L-Jaramillo 1990	0/22	4/34		0.7 %	0.17 [0.01, 2.99]
S-Ramos 1994	5/29	8/34		4.7 %	0.73 [0.27, 1.99]
Purwar 1996	2/97	6/93		2.1 %	0.32 [0.07, 1.54]
Villar 1990	7/94	20/95		6.6 %	0.35 [0.16, 0.80]
L-Jaramillo 1997	0/125	0/135			Not estimable
Subtotal (95% CI)	**392**	**418**		**14.0 %**	**0.43 [0.24, 0.76]**
Total events: 14 (Calcium), 38 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.89, df = 3 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 2.88 (P = 0.0040)					
2 Studies with =/> 400 participants					
Crowther 1999	10/227	23/229		7.9 %	0.44 [0.21, 0.90]
Belizan 1991	33/527	37/542		14.1 %	0.92 [0.58, 1.44]
CPEP 1997	248/2163	229/2173		25.5 %	1.09 [0.92, 1.29]
WHO 2006	398/4038	436/4042		27.0 %	0.91 [0.80, 1.04]
Kumar 2009	19/273	32/251		11.6 %	0.55 [0.32, 0.94]
Subtotal (95% CI)	**7228**	**7237**		**86.0 %**	**0.86 [0.69, 1.07]**
Total events: 708 (Calcium), 757 (Placebo)					
Heterogeneity: Tau² = 0.03; Chi² = 11.25, df = 4 (P = 0.02); I² =64%					
Test for overall effect: Z = 1.33 (P = 0.18)					
Total (95% CI)	**7620**	**7655**		**100.0 %**	**0.76 [0.60, 0.97]**
Total events: 722 (Calcium), 795 (Placebo)					
Heterogeneity: Tau² = 0.05; Chi² = 20.04, df = 8 (P = 0.01); I² =60%					
Test for overall effect: Z = 2.23 (P = 0.026)					
Test for subgroup differences: Chi² = 4.90, df = 1 (P = 0.03), I² =80%					

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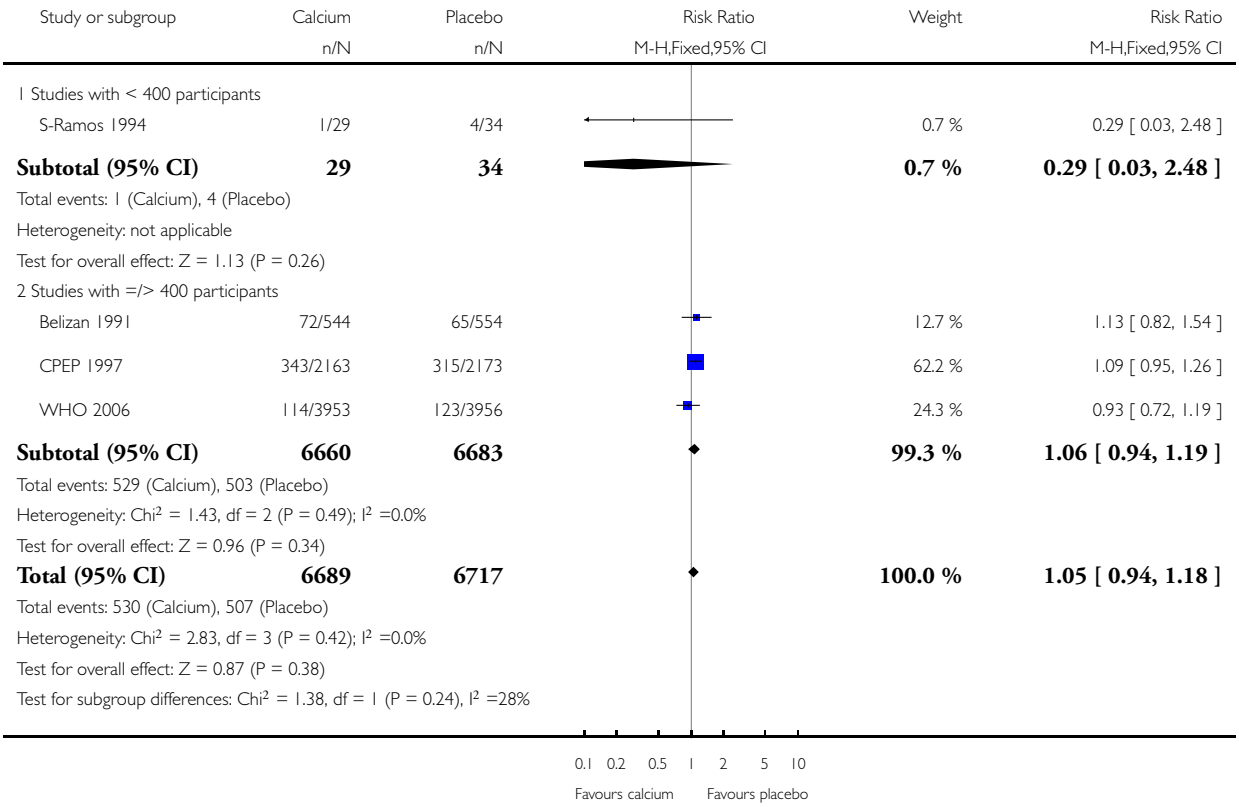
Analysis 3.4. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 4 Admission to neonatal intensive care unit.

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

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

Outcome: 4 Admission to neonatal intensive care unit



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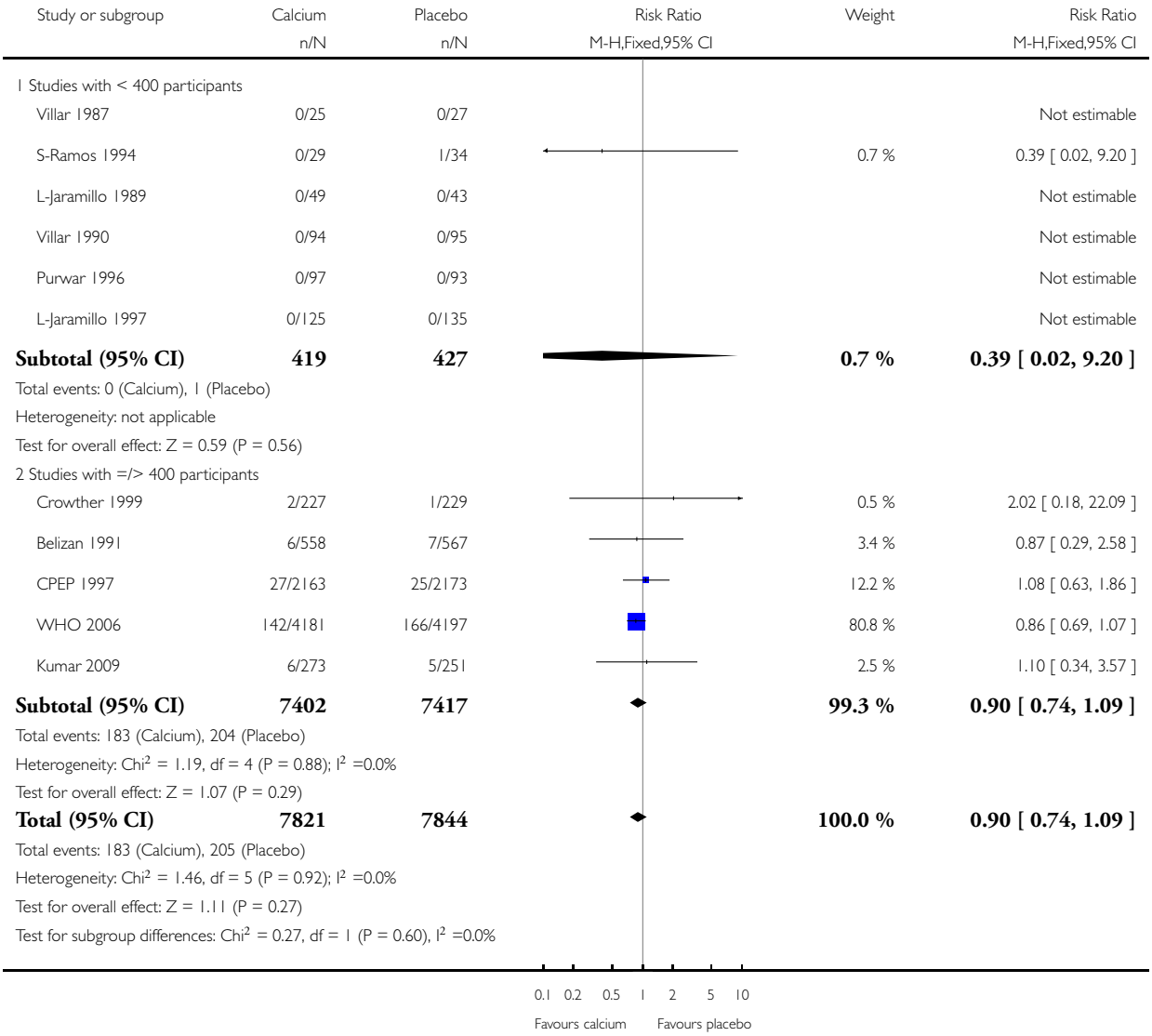
Analysis 3.5. Comparison 3 Routine high-dose calcium supplementation in pregnancy by study sample size, Outcome 5 Stillbirth or death before discharge from hospital.

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

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

Outcome: 5 Stillbirth or death before discharge from hospital



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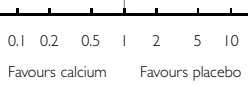
Analysis 4.1. Comparison 4 Routine high-dose calcium supplementation in pregnancy by baseline dietary calcium and study sample size (not pre-specified), Outcome 1 Pre-eclampsia.

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

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

Outcome: 1 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 Adequate calcium/small study					
Villar 1987	1/25	3/27		2.4 %	0.36 [0.04, 3.24]
Villar 1990	0/90	3/88		1.4 %	0.14 [0.01, 2.67]
Subtotal (95% CI)	**115**	**115**		**3.8 %**	**0.26 [0.04, 1.50]**
Total events: 1 (Calcium), 6 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.51 (P = 0.13)					
2 Adequate calcium/large study					
Crowther 1999	10/227	23/229		10.6 %	0.44 [0.21, 0.90]
CPEP 1997	158/2163	168/2173		16.9 %	0.94 [0.77, 1.16]
Subtotal (95% CI)	**2390**	**2402**		**27.5 %**	**0.70 [0.33, 1.46]**
Total events: 168 (Calcium), 191 (Placebo)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 4.04, df = 1 (P = 0.04); I^2 =75%					
Test for overall effect: Z = 0.96 (P = 0.34)					
3 Low calcium/small study					
L-Jaramillo 1990	0/22	8/34		1.6 %	0.09 [0.01, 1.48]
S-Ramos 1994	4/29	15/34		7.8 %	0.31 [0.12, 0.84]
L-Jaramillo 1989	2/55	12/51		4.7 %	0.15 [0.04, 0.66]
Purwar 1996	2/97	11/93		4.6 %	0.17 [0.04, 0.77]
L-Jaramillo 1997	4/125	21/135		7.3 %	0.21 [0.07, 0.58]
Subtotal (95% CI)	**328**	**347**		**26.0 %**	**0.21 [0.12, 0.38]**
Total events: 12 (Calcium), 67 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.26, df = 4 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 5.25 (P < 0.00001)					
4 Low calcium/large study					
Belizan 1991	15/579	23/588		11.6 %	0.66 [0.35, 1.26]
WHO 2006	171/4151	186/4161		17.0 %	0.92 [0.75, 1.13]
Kumar 2009	11/273	30/251		11.2 %	0.34 [0.17, 0.66]
Subtotal (95% CI)	**5003**	**5000**		**39.8 %**	**0.63 [0.35, 1.14]**



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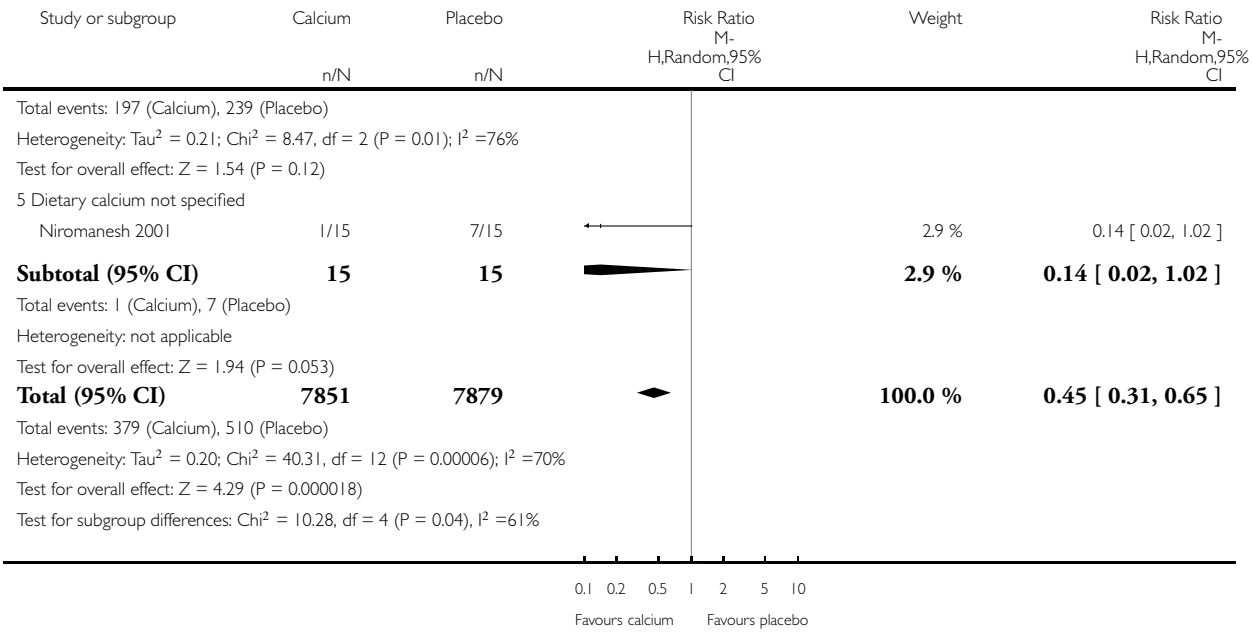
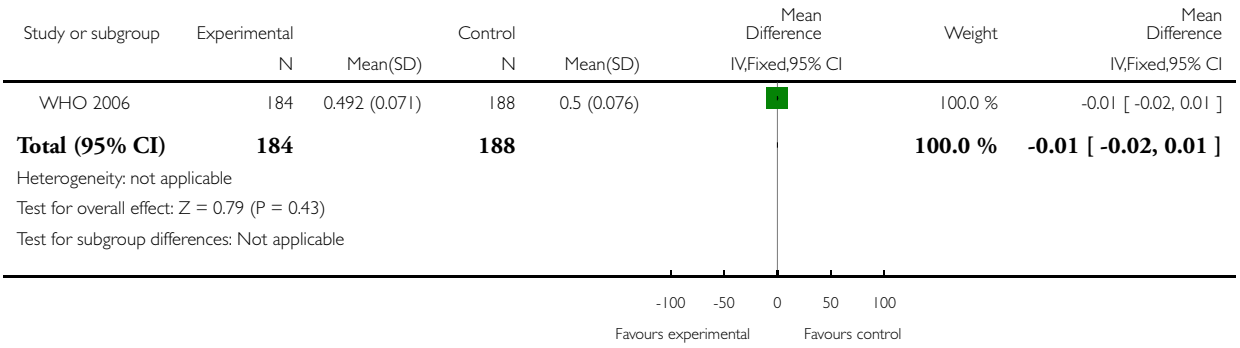


Analysis 5.1. Comparison 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified), Outcome 1 Uterine artery RI at 32 weeks.

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

Outcome: 1 Uterine artery RI at 32 weeks



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

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

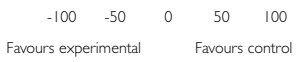
Outcome: 2 Umbilical artery RI at 32 weeks

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
WHO 2006	186	0.655 (0.071)	187	0.66 (0.076)		100.0 %	-0.01 [-0.02, 0.01]
Total (95% CI)	**186**		**187**			**100.0 %**	**-0.01 [-0.02, 0.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable



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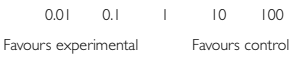
Analysis 5.3. Comparison 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified), Outcome 3 Low platelet count at 35 weeks.

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

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 (1)	20/324	18/343		100.0 %	1.18 [0.63, 2.18]
Total (95% CI)	**324**	**343**		**100.0 %**	**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)					
Test for subgroup differences: Not applicable					



(1) *Reported by Hofmeyr 2008; low platelets defined as <150X10^9/l

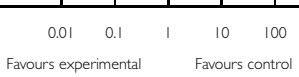
Analysis 5.4. Comparison 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified), Outcome 4 High serum uric acid at 35 weeks.

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

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 (1)	33/322	35/342		100.0 %	1.00 [0.64, 1.57]
Total (95% CI)	**322**	**342**		**100.0 %**	**1.00 [0.64, 1.57]**
Total events: 33 (Experimental), 35 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 1.0)					
Test for subgroup differences: Not applicable					



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(1) *Reported by Hofmeyr 2008; high uric acid defined as >0.32 mmol/L

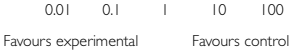
Analysis 5.5. Comparison 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified), Outcome 5 High urine protein/creatinine ratio at 35 weeks.

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

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 (1)	71/308	75/329		100.0 %	1.01 [0.76, 1.34]
Total (95% CI)	**308**	**329**		**100.0 %**	**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)					
Test for subgroup differences: Not applicable					



(1) *Reported by Hofmeyr 2008; high protein/creatinine ratio defined as >34mg/mmol

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

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

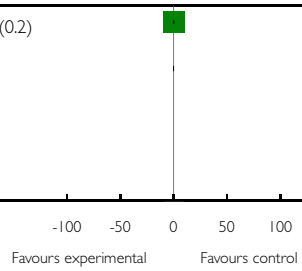
Outcome: 6 Ultrasound estimate of fetal growth at 32 weeks: femur length (cm)*

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
WHO 2006 (1)	186	6.2 (0.2)	191	6.2 (0.2)		100.0 %	0.0 [-0.04, 0.04]
Total (95% CI)	**186**		**191**			**100.0 %**	**0.0 [-0.04, 0.04]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



(1) *Reported by Abalos 2010

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

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

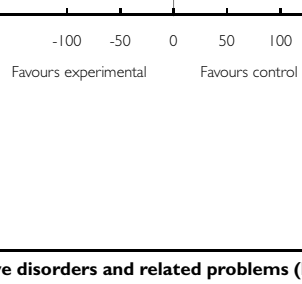
Outcome: 7 Ultrasound estimate of fetal growth at 32 weeks: biparietal diameter (cm)*

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
WHO 2006 (1)	186	8 (0.3)	191	8 (0.3)		100.0 %	0.0 [-0.06, 0.06]
Total (95% CI)	**186**		**191**			**100.0 %**	**0.0 [-0.06, 0.06]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



(1) *Reported by Abalos 2010

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

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

Comparison: 5 Routine calcium supplementation in pregnancy by other outcomes (not pre-specified)

Outcome: 8 Ultrasound estimate of fetal growth at 32 weeks: abdominal circumference (cm)*

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
WHO 2006 (1)	186	27.9 (1.3)	191	27.9 (1.3)		100.0 %	0.0 [-0.26, 0.26]
Total (95% CI)	**186**		**191**			**100.0 %**	**0.0 [-0.26, 0.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Test for subgroup differences: Not applicable							

(1) *Reported by Abalos 2010

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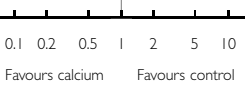
Analysis 6.1. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 1 High blood pressure (with or without pre-eclampsia).

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 1 High blood pressure (with or without 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
1 Calcium supplementation alone					
Bassaw 1998	7/84	12/87		15.5 %	0.60 [0.25, 1.46]
Cong 1995	9/112	10/56		17.6 %	0.45 [0.19, 1.04]
Rogers 1999	29/144	25/75		43.3 %	0.60 [0.38, 0.95]
Subtotal (95% CI)	**340**	**218**		**76.5 %**	**0.57 [0.39, 0.82]**
Total events: 45 (Calcium), 47 (Control)					
Heterogeneity: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 3.01 (P = 0.0026)					
2 Calcium plus vitamin D					
Li 2000	5/29	8/30		10.4 %	0.65 [0.24, 1.75]
Subtotal (95% CI)	**29**	**30**		**10.4 %**	**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)					
3 Calcium plus linoleic acid					
Herrera 2006	2/24	10/24		13.2 %	0.20 [0.05, 0.82]
Subtotal (95% CI)	**24**	**24**		**13.2 %**	**0.20 [0.05, 0.82]**
Total events: 2 (Calcium), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.24 (P = 0.025)					
Total (95% CI)	**393**	**272**		**100.0 %**	**0.53 [0.38, 0.74]**
Total events: 52 (Calcium), 65 (Control)					
Heterogeneity: Chi^2 = 2.55, df = 4 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 3.76 (P = 0.00017)					
Test for subgroup differences: Chi^2 = 2.11, df = 2 (P = 0.35), I^2 =5%					



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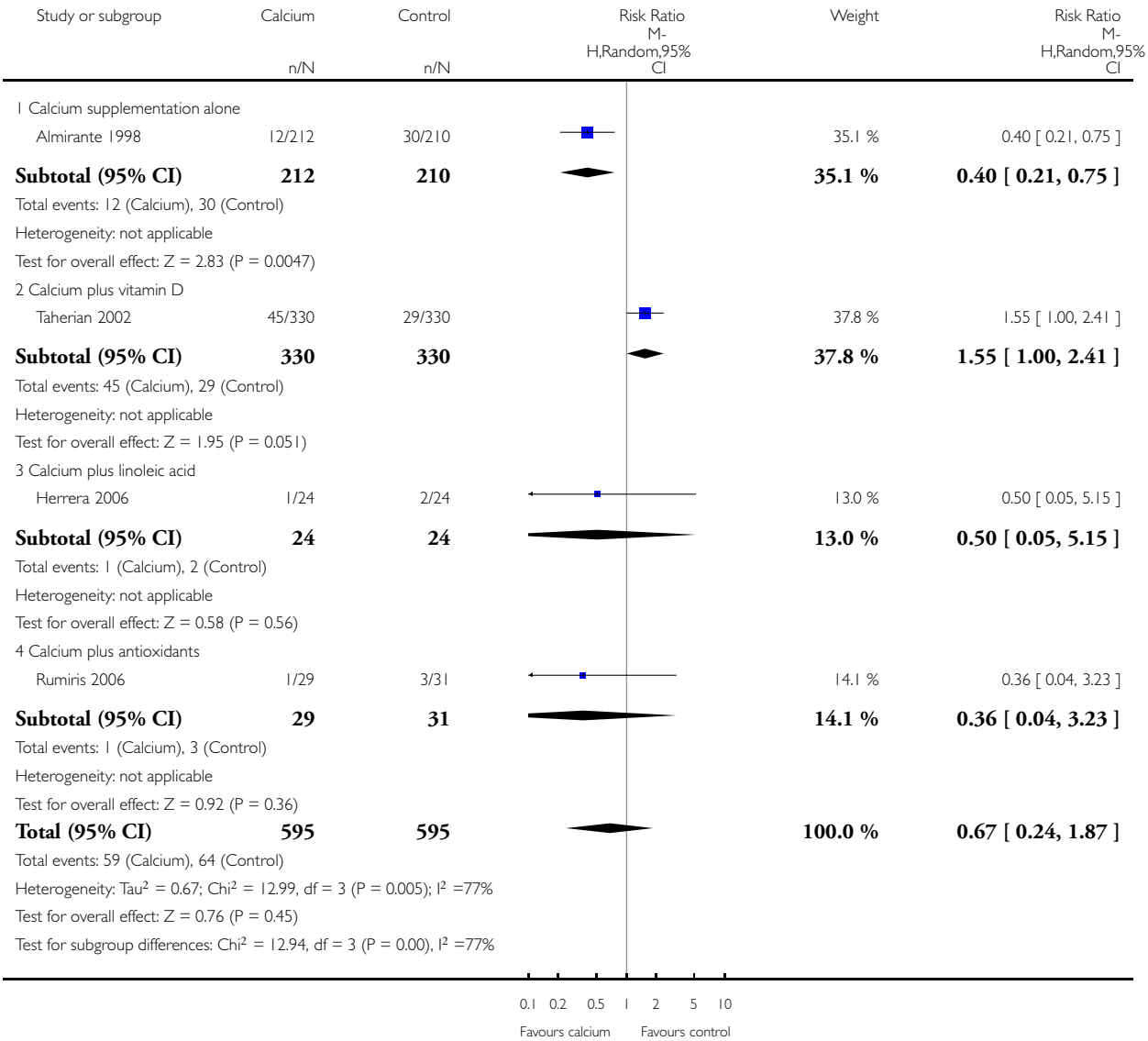
Analysis 6.2. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 2 Preterm birth.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 2 Preterm birth



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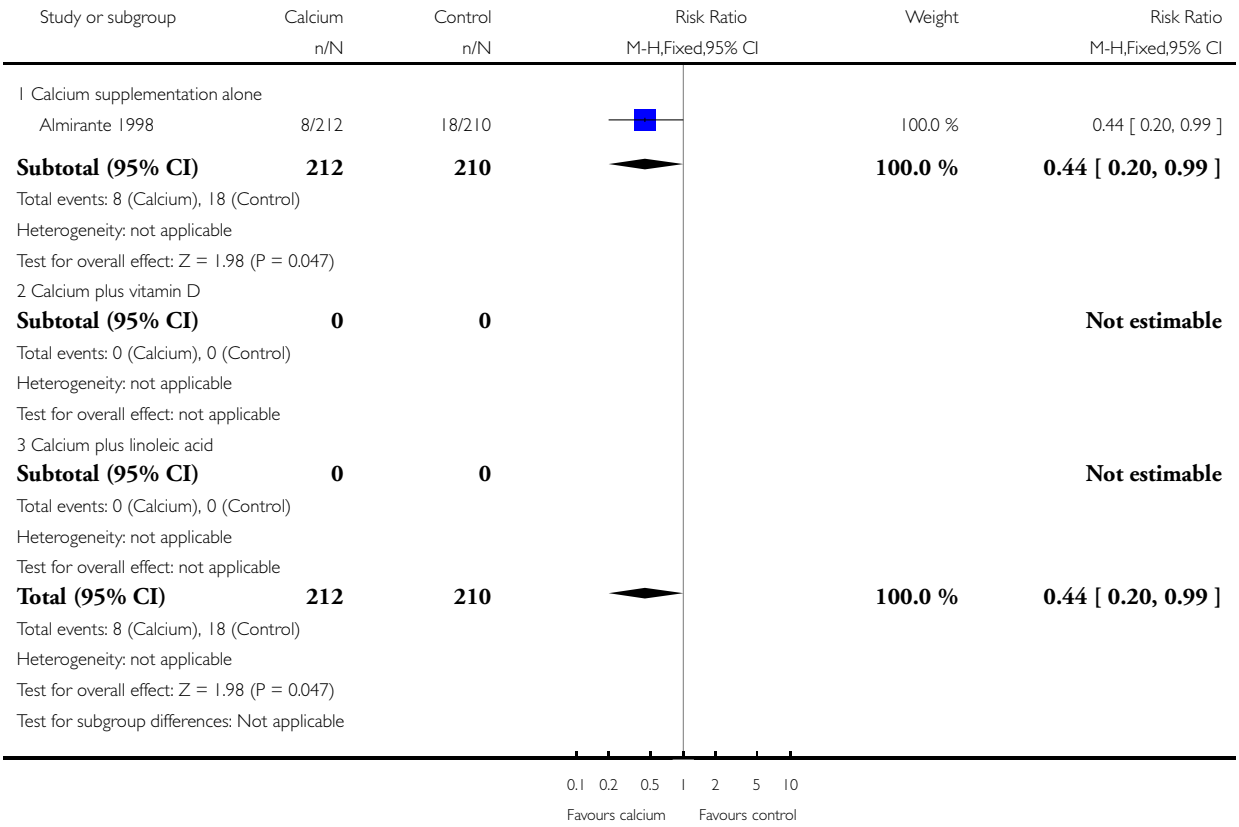
Analysis 6.3. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 3 Neonatal intensive care unit admission.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 3 Neonatal intensive care unit admission



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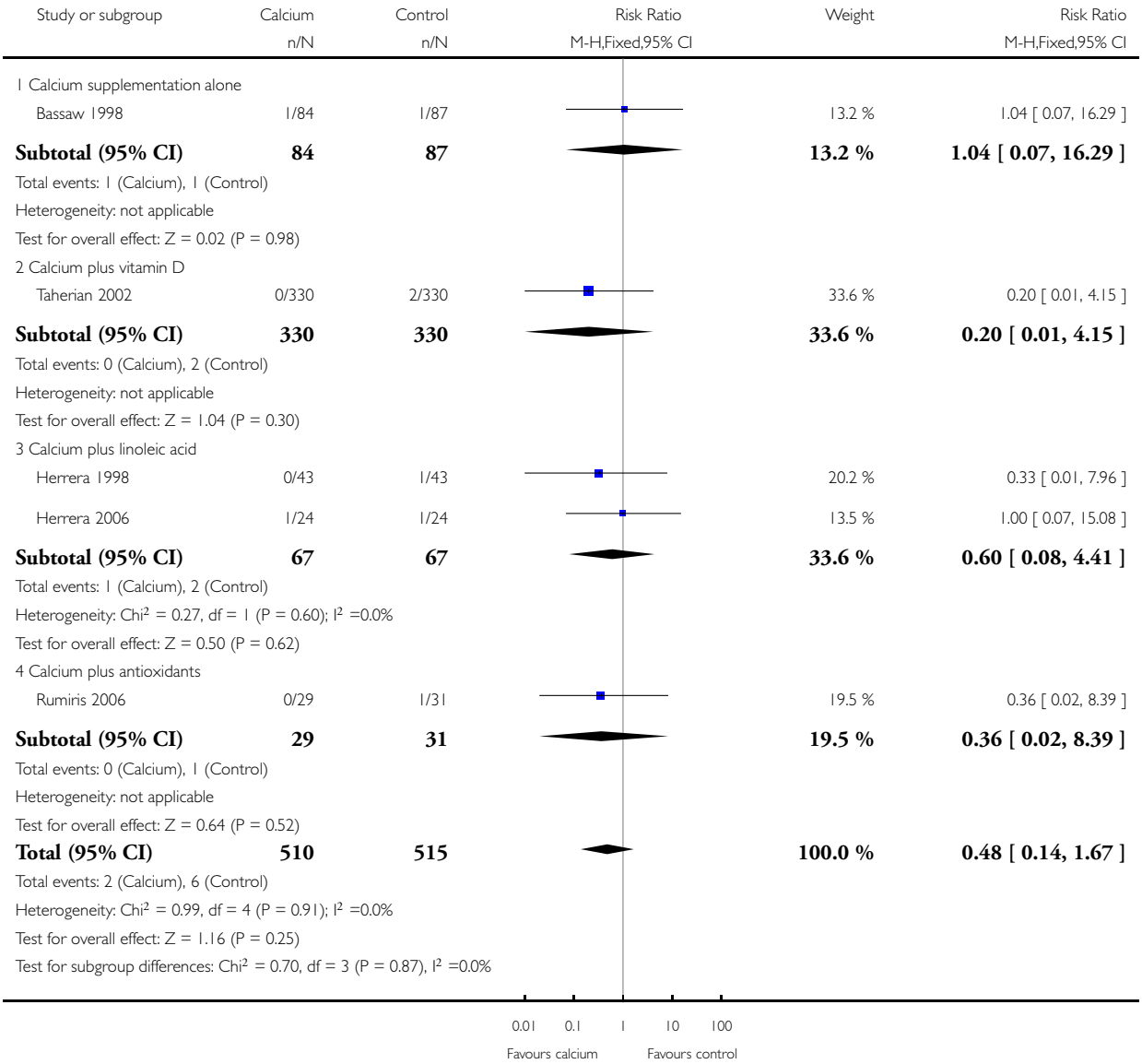
Analysis 6.4. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 4 Stillbirth or death before discharge.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 4 Stillbirth or death before discharge



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Analysis 6.5. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 5 Placental abruption.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 5 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
1 Calcium plus antioxidants					
Rumiris 2006	0/29	0/31			Not estimable
Total (95% CI)	**29**	**31**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

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Analysis 6.6. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 6 Caesarean section.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 6 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
1 Calcium supplementation alone					
Cong 1995	26/112	21/56		29.1 %	0.62 [0.38, 1.00]
Rogers 1999	34/144	12/75		24.8 %	1.48 [0.81, 2.68]
Subtotal (95% CI)	**256**	**131**		**53.9 %**	**0.94 [0.40, 2.22]**
Total events: 60 (Calcium), 33 (Control)					
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 5.09$, df = 1 (P = 0.02); $I^2 = 80\%$					
Test for overall effect: Z = 0.15 (P = 0.88)					
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					
3 Calcium plus linoleic acid					
Herrera 2006	8/24	14/24		22.7 %	0.57 [0.30, 1.10]
Herrera 1998	10/43	19/43		23.4 %	0.53 [0.28, 1.00]
Subtotal (95% CI)	**67**	**67**		**46.1 %**	**0.55 [0.35, 0.87]**
Total events: 18 (Calcium), 33 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.57 (P = 0.010)					
Total (95% CI)	**323**	**198**		**100.0 %**	**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); $I^2 = 60\%$					
Test for overall effect: Z = 1.35 (P = 0.18)					
Test for subgroup differences: $Chi^2 = 1.17$, df = 1 (P = 0.28), $I^2 = 15\%$					

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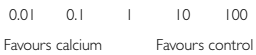
Analysis 6.7. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 7 Severe pre-eclampsia.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 7 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
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					
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					
3 Calcium plus linoleic acid					
Herrera 1998	2/43	6/43		67.4 %	0.33 [0.07, 1.56]
Subtotal (95% CI)	**43**	**43**		**67.4 %**	**0.33 [0.07, 1.56]**
Total events: 2 (Calcium), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
4 Calcium plus antioxidants					
Rumiris 2006	1/29	3/31		32.6 %	0.36 [0.04, 3.23]
Subtotal (95% CI)	**29**	**31**		**32.6 %**	**0.36 [0.04, 3.23]**
Total events: 1 (Calcium), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
Total (95% CI)	**72**	**74**		**100.0 %**	**0.34 [0.10, 1.21]**
Total events: 3 (Calcium), 9 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.095)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.96), I^2 =0.0%					



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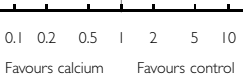
Analysis 6.8. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 8 Pre-eclampsia.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 8 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
1 Calcium supplementation alone					
Bassaw 1998	2/84	7/87		4.9 %	0.30 [0.06, 1.38]
Rogers 1999	8/144	7/75		6.6 %	0.60 [0.22, 1.58]
Cong 1995	0/112	2/56		2.4 %	0.10 [0.00, 2.07]
Almirante 1998	14/212	41/210		29.5 %	0.34 [0.19, 0.60]
Subtotal (95% CI)	**552**	**428**		**43.3 %**	**0.36 [0.23, 0.57]**
Total events: 24 (Calcium), 57 (Control)					
Heterogeneity: Chi^2 = 1.81, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 4.34 (P = 0.000014)					
2 Calcium plus vitamin D					
Marya 1987	12/200	18/200		12.9 %	0.67 [0.33, 1.35]
Taherian 2002	13/330	33/330		23.6 %	0.39 [0.21, 0.73]
Subtotal (95% CI)	**530**	**530**		**36.5 %**	**0.49 [0.31, 0.78]**
Total events: 25 (Calcium), 51 (Control)					
Heterogeneity: Chi^2 = 1.21, df = 1 (P = 0.27); I^2 =17%					
Test for overall effect: Z = 3.02 (P = 0.0026)					
3 Calcium plus linoleic acid					
Herrera 1998	4/43	16/43		11.4 %	0.25 [0.09, 0.69]
Herrera 2006	0/24	3/24		2.5 %	0.14 [0.01, 2.62]
Subtotal (95% CI)	**67**	**67**		**13.9 %**	**0.23 [0.09, 0.60]**
Total events: 4 (Calcium), 19 (Control)					
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 3.01 (P = 0.0026)					
4 Calcium plus antioxidants					
Rumiris 2006	2/29	9/31		6.2 %	0.24 [0.06, 1.01]
Subtotal (95% CI)	**29**	**31**		**6.2 %**	**0.24 [0.06, 1.01]**
Total events: 2 (Calcium), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.95 (P = 0.051)					
Total (95% CI)	**1178**	**1056**		**100.0 %**	**0.38 [0.28, 0.52]**
Total events: 55 (Calcium), 136 (Control)					
Heterogeneity: Chi^2 = 5.76, df = 8 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 6.28 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.66, df = 3 (P = 0.45), I^2 =0.0%					



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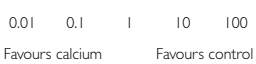
Analysis 6.9. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 9 Eclampsia.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

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
1 Calcium supplementation alone					
Cong 1995	0/112	1/56		100.0 %	0.17 [0.01, 4.06]
Subtotal (95% CI)	**112**	**56**		**100.0 %**	**0.17 [0.01, 4.06]**
Total events: 0 (Calcium), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
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					
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 %**	**0.17 [0.01, 4.06]**
Total events: 0 (Calcium), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Not applicable					



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Analysis 6.10. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 10 Miscarriage.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

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
1 Calcium plus antioxidants					
Rumiris 2006	0/29	8/31		100.0 %	0.06 [0.00, 1.04]
Total (95% CI)	**29**	**31**		**100.0 %**	**0.06 [0.00, 1.04]**
Total events: 0 (Calcium), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.053)					
Test for subgroup differences: Not applicable					

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Analysis 6.11. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 11 Birthweight < 2500 g.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 11 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
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					
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					
3 Calcium plus linoleic acid					
Herrera 1998	1/43	5/43		50.0 %	0.20 [0.02, 1.64]
Herrera 2006	1/24	5/24		50.0 %	0.20 [0.03, 1.59]
Subtotal (95% CI)	**67**	**67**		**100.0 %**	**0.20 [0.05, 0.88]**
Total events: 2 (Calcium), 10 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 2.14 (P = 0.033)					
Total (95% CI)	**67**	**67**		**100.0 %**	**0.20 [0.05, 0.88]**
Total events: 2 (Calcium), 10 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 2.14 (P = 0.033)					
Test for subgroup differences: Not applicable					

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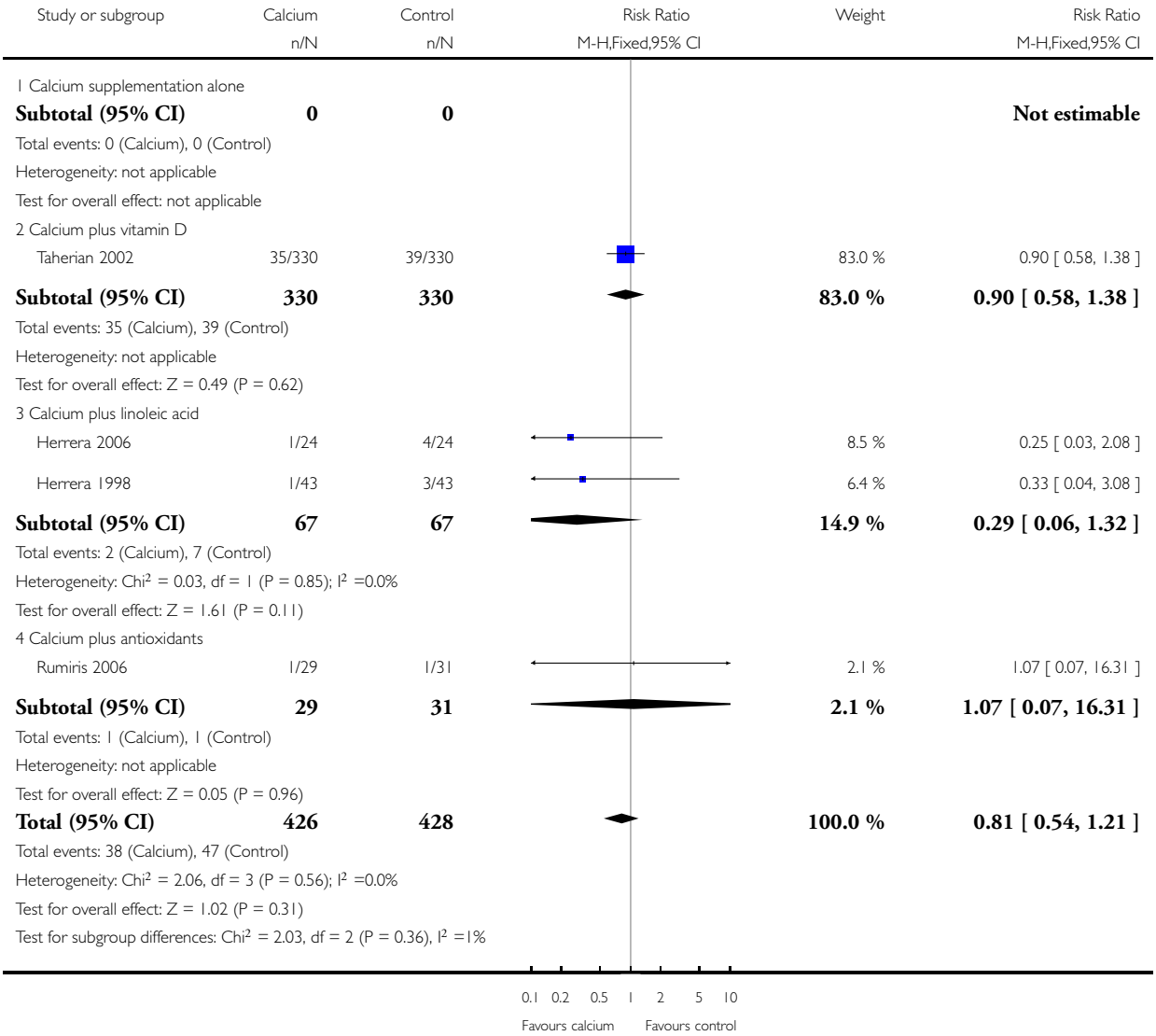
Analysis 6.12. Comparison 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements, Outcome 12 Neonate small-for-gestational age.

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

Comparison: 6 Low-dose calcium supplementation (< 1 g/day) with or without co-supplements

Outcome: 12 Neonate small-for-gestational age



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APPENDICES

Appendix 1. Searches carried out in previous version 2010

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (May 2010). Tne Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We included additional information obtained from the authors in the previous version of this review (Duley 1995) for five studies (Belizan 1991; L-Jaramillo 1989; Marya 1987; Villar 1987; Villar 1990). We obtained additional information from the authors of the new inclusion (Kumar 2009).

We did not apply any language restrictions.

Appendix 2. Methods used in previous version 2010

For this update (2010) we used the following methods when assessing the trials identified by the updated search.

Two review authors independently assessed the methodological quality and other inclusion criteria of the identified trials. We resolved disagreements by consensus. The primary assessment for inclusion was based on concealment of allocation and whether the trial was placebo-controlled.

Two authors independently extracted and cross-checked the data. Descriptive data included authors, year of publication, country, time span of the trial, maternal age, parity, type of placebo, baseline dietary calcium intake, type, dose, onset and duration of calcium supplementation, compliance, co-interventions, trial quality assessments, and number randomised and analysed.

We compared categorical data using risk ratios and their 95% confidence intervals. We tested for statistical heterogeneity among trials using the I^2 statistic, with values greater than 50% indicating significant heterogeneity. In the absence of significant heterogeneity, we pooled data using a fixed-effect model. For continuous data, we calculated pooled estimates of effect size from a weighted average, with weight based on the inverse of the variance (Early Breast Cancer Trialists' Group 1990). We identified comparisons, outcomes and subgroups other than those prespecified in the original protocol as 'post hoc' analyses.

Selection of studies

Two review authors (TA Lawrie (TAL) and GJ Hofmeyr (GJH)) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We would have resolved any disagreement through discussion or, if required, by consulting L Duley (LD).

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Data extraction and management

We designed a form to extract data. For eligible studies, TAL and GJH extracted the data using the agreed form. We would have resolved discrepancies through discussion or, if required, by consulting LD. We entered data into Review Manager software (RevMan 2008) and checked it for accuracy.

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

Assessment of risk of bias in included studies

TAL and GJH independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We resolved any disagreement by discussion.

(1) Sequence generation (checking for possible selection bias)

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

We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

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

We described for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study 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 could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, 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 have re-included missing data in the analyses which we undertook. The cut-off level of missing data that was used to assess that a study is adequate was 20%. We assessed methods as:

- adequate;
- inadequate;
- unclear.

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(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias, e.g. whether the trial was stopped early due to some data-dependent process, whether there was extreme baseline imbalance or whether there was a potential source of bias related to the specific study design.

We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(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 *Handbook* (Higgins 2009). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome but used different methods.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials would be included in the analyses along with individually-randomised trials. We would adjust their sample sizes using the methods described in the Handbook (section 16.3.4) 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 used ICCs from other sources, we would report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually-randomised trials, we would synthesise the relevant information. We would consider it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

We would acknowledge heterogeneity in the randomisation unit and perform sensitivity analyses to investigate the effects of the randomisation unit.

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Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, 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, and all participants would be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. 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 T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P-value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

We investigated reporting biases (such as publication bias) by doing a subgroup analysis based on the sample sizes of the trials.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). 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 is considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we would discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we would not combine trials.

When we used random-effects analyses, the results were presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

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 sizes.

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

For fixed-effect inverse variance meta-analyses we assessed differences between subgroups by interaction tests. For random-effects, we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We undertook sensitivity analysis by considering the results of the larger sample size trials versus the overall results for primary outcomes.

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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.

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(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

Last assessed as up-to-date: 24 May 2013.

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 2012; Diogenes 2013; Goldberg 2013; Herrera 2006a; Jarjou 2013; Sulovic 2013).
28 March 2013	New search has been performed	Search updated. Methods updated.

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 3, 1998

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Date	Event	Description
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 citation required and conclusions have changed	A large trial of calcium supplementation in communities with low dietary calcium intake has been added (WHO 2006).
2 March 2006	New search has been performed	Search updated.

CONTRIBUTIONS OF AUTHORS

Lelia Duley prepared the original review in the Oxford Database of Perinatal Trials.

Álvaro Atallah and Justus Hofmeyr prepared the protocol for the original Cochrane review.

Justus Hofmeyr prepared the initial data analysis 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, Lelia Duley 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. All authors approved the final review.

DECLARATIONS OF INTEREST

Justus Hofmeyr is a collaborator in the WHO Calcium Trial (WHO 2006), which was included in this review.

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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

Additional outcomes were added in 2004, and clearly identified.

The protocol was updated in 2012 and the updates clearly identified.

Protocol amendments September 2012

We have made the following protocol amendments for this 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:
   - quasi-randomised trials (by alternation, unstated method of allocation or other quasi-random methods);
   - trials without placebo control;
   - trials of calcium plus additional supplements (e.g. vitamin D, linoleic acid, or anti-platelet agents).

We included subgroup analysis by trial quality and co-interventions.

INDEX TERMS

Medical Subject Headings (MeSH)

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

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MeSH check words

Female; Humans; Pregnancy

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