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Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes (Review)

Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M, Medley N

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[Intervention Review]

Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes

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ABSTRACT

Background

Maternal nutrition during pregnancy is known to have an effect on fetal growth and development. It is recommended that women increase their calcium intake during pregnancy and lactation, although the recommended dosage varies among professionals. Currently, there is no consensus on the role of routine calcium supplementation for pregnant women other than for preventing or treating hypertension.

Objectives

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcomes (other than for preventing or treating hypertension) as well as any possible side effects.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30th September 2014).

Selection criteria

We considered all published, unpublished and ongoing randomised controlled trials (RCTs) comparing maternal, fetal and neonatal outcomes in pregnant women who received calcium supplementation versus placebo or no treatment. Cluster-RCTs were eligible for inclusion but none were identified. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

Twenty-five studies met the inclusion criteria, but only 23 studies contributed data to the review. These 23 trials recruited 18,587 women, with 17,842 women included in final analyses. There were no statistically significant differences between women who received calcium supplementation and those who did not in terms of reducing preterm births less than 37 weeks' gestation (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.70 to 1.05; 13 studies, 16,139 women; random-effects model) or less than 34 weeks' gestation (RR 1.04, 95% CI 0.80 to 1.36; four trials, 5669). Most studies were of low risk of bias. We conducted sensitivity analysis for the outcome of preterm birth less than 37 weeks by removing two trials with unclear risk of bias for allocation concealment; the results then favoured treatment with calcium supplementation (RR 0.80, 95% CI 0.65 to 0.99; 11 trials, 15,379 women). There was no significant difference in infant low birthweight

between the two treatment groups (RR 0.93, 95% CI 0.81 to 1.07; six trials, 14,162 infants; random-effects model). However, when compared to the control group, women in the calcium supplementation group gave birth to slightly heavier birthweight infants (mean difference 56.40, 95% CI 13.55 to 99.25; 21 trials, 9202 women; random-effects model).

Three outcomes were chosen for assessment with the GRADE software: preterm birth less than 37 weeks; preterm birth less than 34 weeks; and low birthweight less than 2500 g. Evidence for these outcomes was assessed as of moderate quality.

Authors' conclusions

This review indicates that there are no clear additional benefits to calcium supplementation in prevention of preterm birth or low infant birthweight. While there was a statistically significant difference of 56 g identified in mean infant birthweight, there was significant heterogeneity identified, and the clinical significance of this difference is uncertain.

PLAIN LANGUAGE SUMMARY

Effect of taking extra calcium (other than preventing or treating high blood pressure) during pregnancy for improving maternal and infant health

Maternal nutrition during pregnancy is known to have a significant effect on fetal growth and development. In our review, regular intake of extra calcium tablets during pregnancy did not improve the number of preterm births or other infant outcomes, except for a slight increase in infant birthweight in the group of women who received calcium supplementation. Most studies included in this review were assessed as of low risk of bias, and evidence for specific outcomes was graded as of moderate quality, Taking calcium supplementation did not appear to have any obvious side effects. Our review included 25 randomised controlled studies, but only 23 studies involving 18,587 women contributed outcome data. The majority of the evidence was based on fewer numbers of studies.

Summary of findings for the main comparison. Calcium supplementation versus placebo or no treatment (maternal outcomes) for preventing or treating hypertension) for improving pregnancy and infant outcomes

Calcium supplementation versus placebo or no treatment for improving pregnancy and infant outcomes

Patient or population: healthy pregnant women receiving calcium supplementation vs placebo or no treatment
Settings: trials located in Australia, Guatemala, India (3), Iran, and the USA (3). A multi-centre study took place in Argentina, Egypt, India, Peru, South Africa, United Kingdom and Vietnam.
Intervention: calcium supplementation versus placebo or no treatment (maternal outcomes)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Calcium supplementation versus placebo or no treatment (maternal outcomes)				
Preterm birth (a) Birth prior to 37 weeks	**Study population**		**RR 0.86** (0.7 to 1.05)	16139 (13 studies)	⊕⊕⊕⊖ **moderate** [1]	We conducted sensitivity analysis by removing 2 trials with unclear risk of bias for allocation concealment; the results then favoured treatment with calcium supplementation (RR 0.80, 95% CI 0.65 to 0.99; 11 trials, 15379 women).
	105 per 1000	**90 per 1000** (73 to 110)				
	Moderate					
	100 per 1000	**86 per 1000** (70 to 105)				
Preterm birth (b) Birth prior to 34 weeks	**Study population**		**RR 1.04** (0.8 to 1.36)	5669 (4 studies)	⊕⊕⊕⊖ **moderate** [1]	
	36 per 1000	**38 per 1000** (29 to 49)				
	Moderate					
	30 per 1000	**31 per 1000** (24 to 41)				
Low birthweight (< 2500 g)	**Study population**		**RR 0.93** (0.81 to 1.07)	14162 (6 studies)	⊕⊕⊕⊖ **moderate** [2]	
	116 per 1000	**108 per 1000**				

	(94 to 125)	
Moderate		
86 per 1000	**80 per 1000** (70 to 92)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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.

[1] Wide confidence interval crossing the line of no effect. (-1)
[2] Statistical heterogeneity ($I^2 > 60\%$). (-1)

BACKGROUND

Description of the condition

Calcium metabolism

Calcium is an essential mineral for many of the body's processes (Trichopoulou 1990). Calcium is a key and important intracellular component for maintaining cell membranes, and has a role in nerve cell function, muscle contraction, enzyme and hormone actions, and is essential for bone mineralisation. Maternal nutrition during pregnancy has a significant effect on fetal growth and development (Luke 1994; Susser 1991). Calcium is transported across the placenta by an active transport process, and is important in many developmental functions, including skeletal development (McGuire 2007).

During pregnancy and lactation women require an increase in their calcium intake (Cross 1995; Ritchie 1998). This is not only to maintain maternal calcium balance and bone density, but also to meet the demands of the growing fetus/infant.

Description of the intervention

Calcium supplementation

The recommendations for calcium intake during pregnancy and lactation vary from 600 mg to 1425 mg per day, up to 600 mg higher than in non-pregnant women (Prentice 1994). Approximately 200 mg of calcium per day is secreted into breast milk (Prentice 1994).

The increase in calcium requirements may be met through dietary intake. However, supplementation of calcium during pregnancy and lactation has been recommended by some, at doses between 300 mg and 2000 mg per day (Belizan 1991; Koo 1999; Raman 1978). For this review, we have arbitrarily divided calcium supplementation into low dose (less than 1000 mg per day) and high dose (1000 mg or more per day) (Jarjou 2006; Kalkwarf 1997;Prentice 1995; Raman 1978; Villar 1990).

Calcium tablets are inexpensive and readily available. However, side effects have been reported, including difficulty in swallowing, an increase in urinary stones and urinary tract infection, as well as reduced absorption of other minerals such as iron, zinc and magnesium (Hallberg 1992; McGuire 2007).

The effect of calcium supplementation on weight is unclear, with some studies identifying a reduction in body weight, possibly through the combination of calcium with fatty acids which are subsequently not absorbed by the body (Heaney 2002; Sampath 2008; Trowman 2006; Yanovski 2009).

How the intervention might work

During pregnancy and lactation, maternal bone mineral density decreases in multiple sites of the body such as the lumbar spine, femoral neck, hip and wrist. However, this is quickly reversed after cessation of breastfeeding (Cross 1995; Kalkwarf 1997; Laskey 1999; Prentice 1995; Sowers 1993; Sowers 1995). Inadequate intake of calcium may harm both the woman and her fetus. Maternal risks of inadequate calcium intake include osteopenia, osteoporosis, tremor, paraesthesia, muscle cramps and tetany (muscle spasm and twitching). Potential problems for the fetus/infant include delayed fetal growth, low birthweight and poor bone mineralisation (Inzucchi 1999; Koo 1999). It is unclear whether calcium supplementation may help women and babies avoid the complications associated with inadequate calcium intake.

Why it is important to do this review

Current approach to calcium supplementation in pregnancy

Currently, there is no consensus on the role of routine calcium supplementation for pregnant women.

A Cochrane review evaluating calcium supplementation for the prevention of pre-eclampsia identified a significant beneficial effect, almost halving the risk of women developing pregnancy-induced hypertension (Hofmeyr 2014). However, the effect of calcium supplementation on other pregnancy and infant outcomes remains uncertain, with some studies identifying a beneficial effect on fetal growth and bone mineralisation (Chan 2006; Chang 2003; Janakiraman 2003), although this is not universal (Jarjou 2006; Prentice 1995). Calcium also plays a role in smooth muscle function, being important in muscle contraction. Some studies have suggested that calcium supplementation may contribute to altered muscle tone and may therefore contribute to the risk of preterm birth (Hofmeyr 2014), although the precise effect is unclear (Belizan 1991; Carroli 1994; Lopez-Jaramillo 1989; Villar 1990; Villar 1998). While there is a clear benefit of calcium supplementation in the prevention of hypertension during pregnancy, the effect on other outcomes requires further evaluation.

OBJECTIVES

To determine the effect of calcium supplementation on maternal, fetal and neonatal outcomes (other than for preventing or treating hypertension), including the occurrence of side effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished and ongoing simple and randomised controlled trials (RCTs) comparing maternal, fetal, and neonatal outcomes in pregnant women who received calcium supplementation compared with placebo or no treatment. Cluster-RCTs were eligible for inclusion but none were identified. Quasi-RCTs and cross-over studies were not eligible for inclusion.

Types of participants

Pregnant women who received any calcium supplementation compared with placebo or no treatment.

Types of interventions

Calcium supplementation during pregnancy compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Preterm birth less than 37 weeks' gestation

Infant outcomes

1. Low birthweight (less than 2500 g)

Secondary outcomes

Maternal outcomes

1. Preterm birth less than 34 weeks' gestation
2. Maternal weight gain
3. Maternal bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (osteopenia is classified as BMD between -1 and -2.5 SD; osteoporosis is classified as BMD less than -2.5 SD)
4. Leg cramps
5. Backache
6. Tetany
7. Incidence of fracture
8. Duration of breastfeeding
9. Tremor
10. Paraesthesia
11. Mother admitted to an intensive care unit
12. Maternal death
13. Mode of birth (vaginal birth, Instrumental vaginal birth, caesarean section)
14. Postpartum haemorrhage

Fetal and neonatal outcomes

1. Stillbirth or fetal death (fetus died in uterus after 20 weeks' gestation or during labour and delivery)
2. Neonatal death (baby died in first 28 days of life)
3. Perinatal mortality (stillbirth and neonatal death)
4. Admission to neonatal intensive care unit
5. Birthweight
6. Birth length
7. Head circumference
8. Intrauterine growth restriction
9. Neonatal BMD (measured by single-photon absorptiometry or dual-energy x-ray absorptiometry)
10. Osteopenia
11. Rickets
12. Fracture

Adverse outcomes

1. Side effects of calcium supplementation
2. Compliance
3. Satisfaction (as defined by the trial authors)
4. Urinary stones
5. Urinary tract infection
6. Nephrocalcinosis
7. Impaired renal function (as defined by the trial authors)
8. Maternal anaemia (as defined by the trial authors)

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2014).

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

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. 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.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* Buppasiri 2011.

For this update, the following methods were used for assessing the 19 reports that were identified as a result of the updated search.

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

Selection of studies

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

Data extraction and management

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

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

Assessment of risk of bias in included studies

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

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

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

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- 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);
- unclear risk of bias.

(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 had about other possible sources of bias.

(7) Overall risk of bias

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

For this update the quality of the evidence was assessed using the GRADE approach (Schunemann 2009). We assessed the quality of the body of evidence relating to the following outcomes.

1. Preterm birth < 37 weeks
2. Preterm birth < 34 weeks
3. Low birthweight (< 2500 g)

GRADE profiler (GRADEpro 2014) was used to import data from Review Manager 5.3 (RevMan 2014) and create a 'Summary of findings' table, or a summary of the intervention effect and a measure of quality for each of the above outcomes. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the

quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

We have not included any cluster-randomised trials in this update. If in future updates we include cluster-randomised trials in the analyses, we will adjust their sample sizes using the methods described in the Handbook *[Section 16.3.4 or 16.3.6]* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

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

Cross-over trials

We have not included cross-over trials in this review and do not consider this design appropriate to answer the review's questions.

Other unit of analysis issues

We have not included multiple pregnancies in this review because multiple pregnancies may have an effect on the outcomes of interest, such as preterm birth, and so studies including multiple pregnancies are not considered eligible for inclusion.

In studies that had more than two treatment groups, we divided the placebo arm between the two treatment arms. Specifically, for the trial Belizan 1983, in Analysis 2.4 and Analysis 2.9, the placebo arm was halved to enable inclusion of data for treatment groups one and two.

Dealing with missing data

For included studies, levels of attrition were noted. In future updates, if more eligible studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis.

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

Assessment of heterogeneity

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

Assessment of reporting biases

Where there were 10 or more studies in the meta-analysis we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

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

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average 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. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

We carried out the following subgroup analyses for maternal primary outcomes.

1. Preterm birth < 37 weeks by dose of calcium (low dose or less than 1000 mg/day versus high dose or 1000 mg/day or more)
2. Preterm birth < 37 weeks by gestational week started to take calcium (before 20 weeks versus 20 weeks or more)

3. Preterm birth < 37 weeks by type of calcium (carbonate versus lactate versus gluconate)

We carried out the following subgroup analyses for Infant primary outcomes.

1. Low birthweight < 2500 g by gestational week started to take calcium (before 20 weeks versus 20 weeks or more)
2. Low birthweight < 2500 g by type of calcium (gluconate versus carbonate)

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

Sensitivity analysis

We planned to carry out the following sensitivity analysis to explore the effect of trial quality assessed by concealment of allocation, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

1. Preterm birth < 37 weeks (adequate allocation concealment versus unclear or no allocation concealment)
2. Preterm birth < 34 weeks (adequate allocation concealment versus unclear or no allocation concealment)
3. Low birthweight (< 2500 g)

We conducted the above sensitivity analysis, apart from the low birthweight outcome because there were no trials at unclear or low risk of bias for allocation concealment contributing data to this outcome.

RESULTS

Description of studies

Results of the search

The original search yielded 72 trial reports (Buppasiri 2011). After exploring the contents and grouping for duplicates, we included data from 21 trials (54 reports). One further trial that was otherwise eligible for inclusion specifically focused on maternal blood lead levels and did not report any other outcomes, and so has not contributed data to the review (Ettinger 2009). We have provided details of this study in Characteristics of included studies but we have not referred to this study in the discussion of included studies below. We excluded 14 trials and four trials were 'Awaiting classification' because only the abstracts were available (Almirante 1998; Chames 2002; Galimberti 2001) - we tried to contact the authors but unfortunately full papers were not available.

For this update, a search in September 2014 identified another 19 reports for eligibility assessment. Three new trials were eligible for inclusion (Goldberg 2013; Herrera 2006; Kumar 2009). Four new reports (related to three trials), one of which requires translation (Zheng 2000), were abstracts and were added to Studies awaiting classification. Six reports were excluded, three of which were duplicates for studies in awaiting classification (Almirante 1998; Chames 2002; Galimberti 2001) and have now been excluded because we have not had replies from authors at the second round of queries. Finally, six further new reports were additional publications for already included studies.

At this update, we now have 25 included studies (63 reports), but only 23 studies contribute outcome data (Herrera 2006 and Ettinger 2009 contribute no outcome data). There are 20 excluded studies (21 reports), and three abstracts that remain in Studies awaiting classification (we have attempted to contact authors but have had no replies). We should note that the newly included Goldberg 2013 reports on the same trial as the previously included Jarjou 2006. Jarjou 2006 analyses a subset of women and reports specific outcomes not included in the much later report on the full sample. We have kept these data separate for clarity.

Included studies

For more information about included studies, *see:* Characteristics of included studies.

Design

All included studies were reported as randomised controlled trials (RCTs), and one trial (Villar 2006) was stratified by country.

Sample size

The total number of participants included in the 23 trials (of the 25 included trials) that contributed data to this review was 18,587 pregnant women, but only 17,842 were included in final analyses. Ettinger 2009 and Herrera 2006 did not contribute to outcome data for this review. Missing data amounted to 4.01% overall (745 in 17,842). The sample size varied from 23 to 8325 participants per trial.

Setting

The 25 included trials took place in various countries: Argentina, Australia, Columbia, Egypt, Ecuador, Gambia, Guatemala, Hong Kong, India, Iran, Mexico, South Africa, United States and Vietnam.

Participants

This review includes data for 18,578 pregnant women. Three trials (Chan 2006; Herrera 2006; Villar 1990) included only adolescent pregnant women (309 women, mean age 17.0 years), but the remaining trials were not restricted to adolescents. Two trials (Jarjou 2006; Raman 1978) included only pregnant women from low socioeconomic groups. The largest study (Villar 2006 with 8325 women) recruited only pregnant women who received less than 600 mg dietary calcium per day. One study (Lopez-Jaramillo 1997) included pregnant women who had lived at an altitude of 2800 m for a period of at least one year. One study (Sanchez-Ramos 1994) enrolled pregnant women who had normotension but positive roll-over and angiotensin tests.

Interventions

Calcium supplementation was used in the treatment groups in all trials and compared with placebo or no treatment control groups. Various types of calcium were used such as calcium carbonate, calcium gluconate, calcium lactate and combined calcium. Calcium carbonate was prescribed in most studies (in 17 of the 23 trials). Calcium lactate was prescribed in one trial and calcium gluconate was prescribed in one trial. Combined calcium supplementation was prescribed in two trials and three trials did not specify the type of calcium used. For timing of calcium supplementation; 11 trials (Belizan 1991; Boggess 1997; Crowther 1999; Goldberg 2013; Jarjou 2006; Karandish 2003; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1995; Taherian 2002; Villar 1990) started calcium

supplementation at 20 weeks' gestational age (or after) until delivery. Five trials (Belizan 1983; Chan 2006; Kumar 2009; Levine 1997; Villar 2006) started calcium supplementation at gestational age less than 20 weeks until delivery. Timing was unclear in the remaining studies. For dosage of calcium, 14 trials (Belizan 1991; Boggess 1997; Crowther 1999; Goldberg 2013; Jarjou 2006; Karandish 2003; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1990; Villar 2006) prescribed 1000 mg/d or more (range 1000 to 2000 mg/d). Three trials (Raman 1978; Rogers 1999; Taherian 2002) prescribed calcium less than 1000 mg/day (range 300 mg to 600 mg). In the Taherian 2002 study, calcium supplementation (Caltrate) was prescribed 600 mg at 22 to 32 weeks' gestational age and then 1200 mg from 32 weeks until delivery.

Outcomes

The primary outcomes or objectives of 16 of the 23 trials that contributed data to this review were incidence of pregnancy induced hypertension or changes in blood pressure, which were not relevant to this review. However, these studies also reported other outcome data relevant to this review, e.g. preterm birth, maternal weight gain, gestational age, birthweight, birth length, and we have therefore included these data. Thirteen trials with a total of 16,139 participants (Belizan 1991; Boggess 1997; Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1990; Villar 2006; Wanchu 2001) evaluated the effect of calcium supplementation on preterm birth before 37 weeks. Four trials, with 5669 participants (Crowther 1999; Kumar 2009; Levine 1997; Wanchu 2001) evaluated the effect of calcium supplementation on preterm birth before 34 weeks. Six of the trials with 14,162 participants (Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Villar 1990; Villar 2006) evaluated the effect of calcium supplementation on low birthweight (less than 2500 g). Seven trials (Belizan 1991; Crowther 1999; Levine 1997; Villar 1987; Villar 1990; Villar 2006; Wanchu 2001) evaluated side effects of calcium supplementation. For further details, *see* Characteristics of included studies.

No trials reported the effect of calcium supplementation on leg cramps, backache, tetany, tremor, paraesthesia, osteopenia, osteoporosis, fracture in pregnant women, duration of breastfeeding or postpartum haemorrhage, and no trials reported on fetal or neonatal osteopenia, rickets and fracture.

Excluded studies

We excluded 20 trials from this review. The reasons for exclusion include: participants, interventions and methodology were not appropriate and there was insufficient information for inclusion. For more information, *see* Characteristics of excluded studies. For more information about the studies which we have not yet assessed for inclusion, *see* Characteristics of studies awaiting classification.

Risk of bias in included studies

The number of participants in trials ranged from 23 to 8325 per trial.The risk of bias in included studies varied. The overall missing data (lost to final analysis) were 4.01% (745 in 17842) ranging from (0% to 68.1%). Seven of the 23 trials contributing data had no missing data. Ten of the 23 trials had missing data less than 10%. Only one trial had a very high rate of missing data (68.1%). The largest trial had 0.16% missing data. The majority of included studies used methods of sequence generation and allocation concealment which we assessed as being at low risk of bias and overall, the included studies were assessed as low risk of bias for other domains of methodological quality. For an overview of review authors' judgments about each 'Risk of bias' item for individual included studies, *see* Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

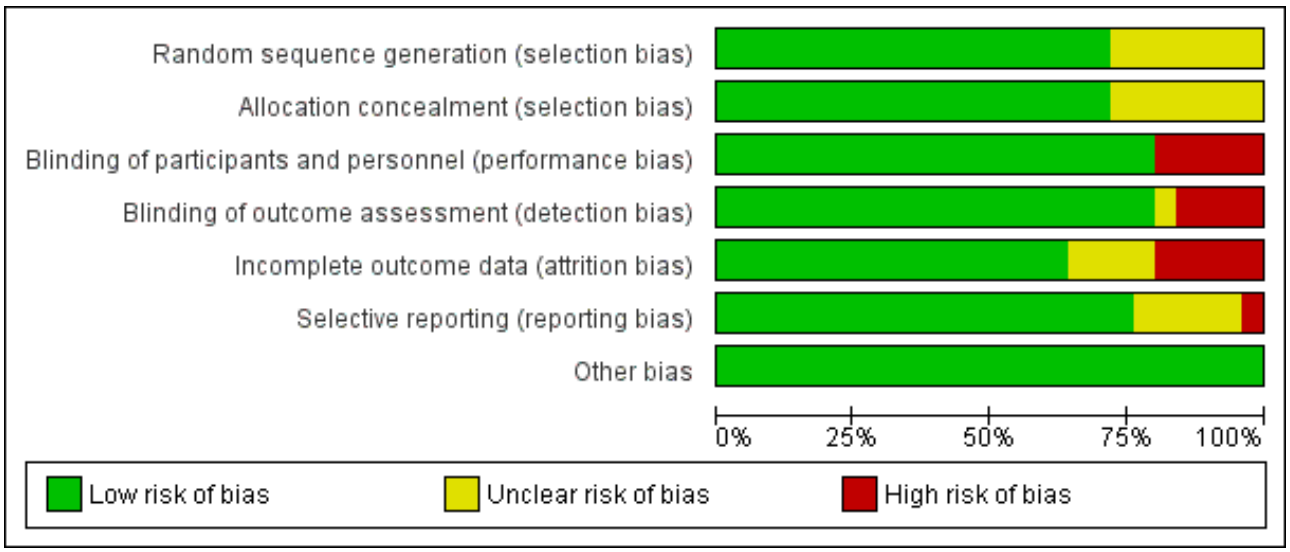


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

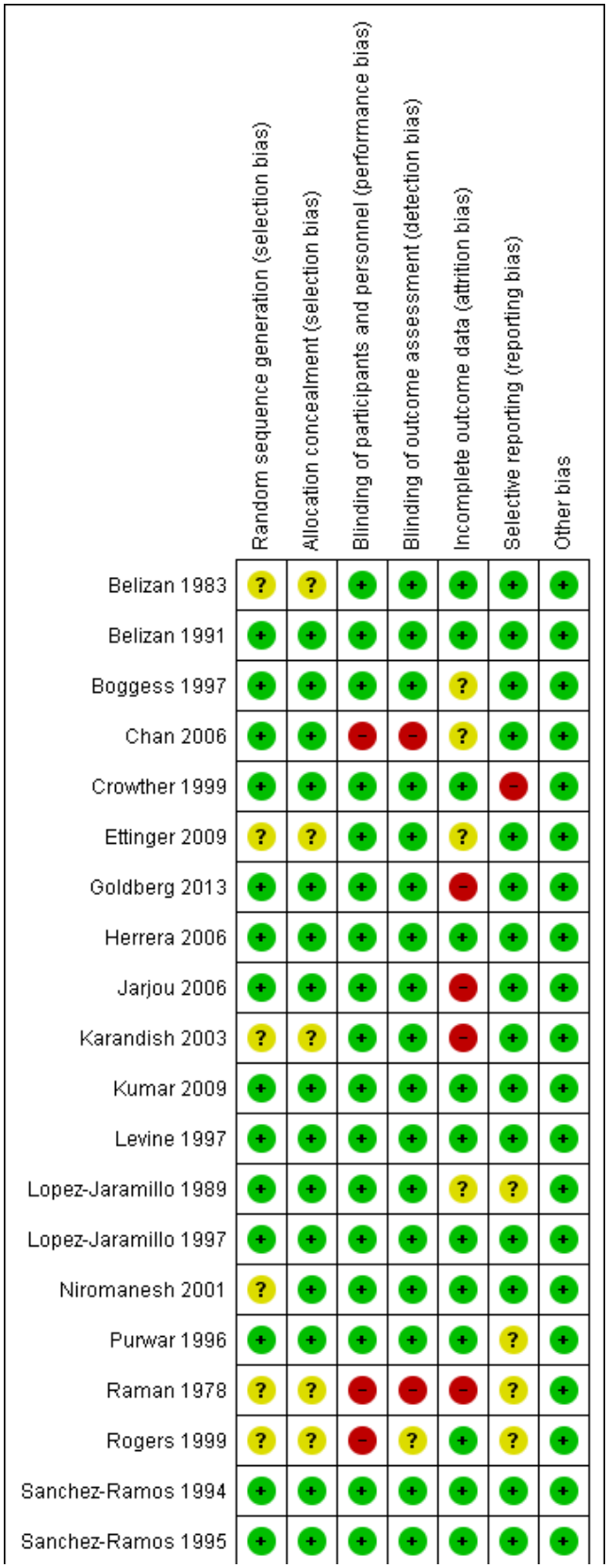
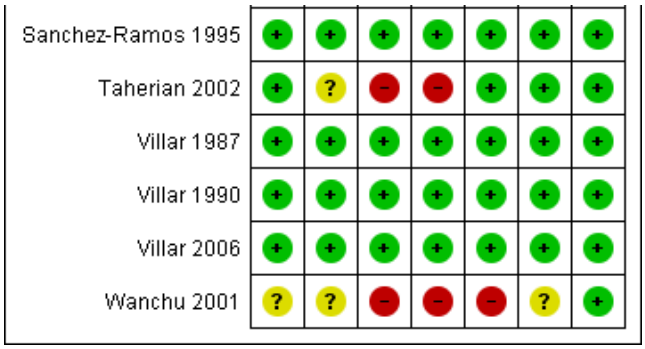


Figure 2. (Continued)



Allocation

All studies included in this review were reported as being RCTs. Sample size calculation was clearly stated in only one trial (Crowther 1999). However, the two largest trials (Levine 1997; Villar 2006) had good methodological quality. Sequence generation was clearly described in 18 trials rated as 'low risk of bias' (Belizan 1991; Boggess 1997; Chan 2006; Crowther 1999; Goldberg 2013; Herrera 2006; Jarjou 2006; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1987; Villar 1990; Villar 2006). The remaining studies did not describe how the randomisation sequence was generated and were assessed as of unclear risk (Belizan 1983; Ettinger 2009; Karandish 2003; Niromanesh 2001;Raman 1978; Rogers 1999; Wanchu 2001).

Adequate allocation concealment was reported in 18 trials, and these were rated as 'low risk of bias' (Belizan 1991; Boggess 1997; Chan 2006; Crowther 1999; Goldberg 2013; Herrera 2006; Jarjou 2006; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Niromanesh 2001; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1987; Villar 1990; Villar 2006). The remaining studies did not describe allocation concealment.

Blinding

Most of studies were considered to be of low risk of performance bias and detection bias. Double-blinding was reported in 20 studies (Belizan 1983; Belizan 1991; Boggess 1997; Crowther 1999; Ettinger 2009; Goldberg 2013; Herrera 2006; Jarjou 2006; Karandish 2003; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Niromanesh 2001; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1987; Villar 1990; Villar 2006). One study (Chan 2006) was unable to blind because the groups consumed different food. The four trials using 'no treatment' as the control group were unable to blind the participants (Raman 1978; Rogers 1999; Taherian 2002; Wanchu 2001).

Incomplete outcome data

Most studies reported incomplete outcome data. Intention-to-treat (ITT) analyses was used in 11 trials assessed as of low or unclear risk of attrition bias (Belizan 1983; Belizan 1991; Crowther 1999; Kumar 2009; Lopez-Jaramillo 1989; Niromanesh 2001; Rogers 1999; Taherian 2002; Villar 1987; Villar 1990; Villar 2006). Goldberg 2013 also used ITT analysis, but the attrition rate was 20%; the trial was assessed as high risk of bias. Four additional trials did not use ITT analyses and were assessed as high risk of bias for incomplete outcome data (Jarjou 2006; Karandish 2003: Raman 1978; Wanchu 2001). The remaining trials did not conduct ITT analyses but were assessed as unclear or low risk for attrition bias (Boggess 1997; Chan 2006; Herrera 2006; Lopez-Jaramillo 1997; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; The rate of losses to follow-up varied from 0% to 68.1%.

Selective reporting

We did not have the protocols for all the included studies; therefore we could not fully address selective reporting. Where trials specified their intended outcomes for analyses and then also presented relevant data for all of these outcomes, we assessed the trial as of low risk of bias.

Other potential sources of bias

None identified.

Effects of interventions

See: **Summary of findings for the main comparison** Calcium supplementation versus placebo or no treatment (maternal outcomes) for preventing or treating hypertension) for improving pregnancy and infant outcomes

Comparison: Calcium supplementation versus placebo or no treatment

Primary outcomes

Maternal outcomes

1. Preterm birth less than 37 weeks' gestation

Thirteen trials (Belizan 1991; Boggess 1997; Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1990; Villar 2006; Wanchu 2001) with data for 16,139 women. There were 8074 women who received calcium supplementation and 8065 women who received placebo or no treatment. Meta-analysis evaluating the effect of calcium supplementation versus placebo or no treatment on preterm birth before 37 weeks revealed that there was no statistically significant difference between the two groups (average risk ratio (RR) 0.86, 95% confidence interval (CI) 0.70 to 1.05; random-effects model; Analysis 1.1). However, there was substantial heterogeneity between trials (Tau^2 = 0.05; Chi^2 = 25.60, df = 11 (P = 0.007); I^2 = 57%). Therefore, we explored the source of heterogeneity by subgroup analyses stratified by total dose of calcium per day (less than 1000 mg/day or 1000 mg/day

or more), starting time of calcium supplementation (before or after 20 weeks) and type of calcium (calcium carbonate, lactate and gluconate).

For total dose of calcium per day, there appeared to be a difference between subgroups (Test for subgroup differences: $Chi^2 = 6.93$, df = 1 (P = 0.008), $I^2 = 85.6\%$; Analysis 1.2). However, only one study was included in the low-dose subgroup (Taherian 2002), while 12 studies were in the high-dose subgroup, so this apparent difference between groups may have occurred by chance.

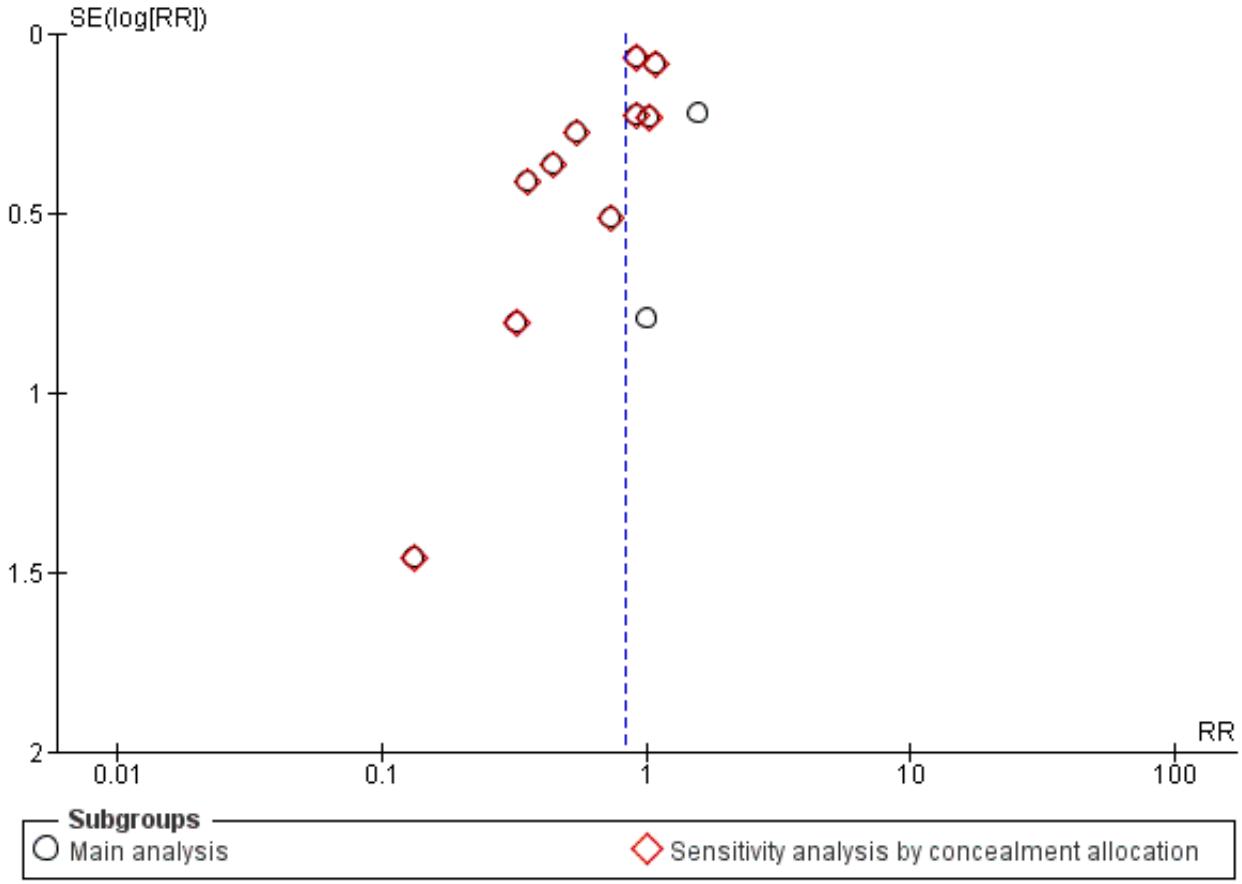
For the starting time of calcium supplementation, we found that there was no statistically significant differences between subgroups for women who started calcium before 20 weeks and for women who started calcium at 20 weeks or more (Analysis 1.3).

For type of calcium, there was no statistically significant difference between subgroups when women received calcium carbonate or calcium gluconate; however only one trial gave calcium gluconate to 92 women and in this study there was no preterm birth before 37 weeks in either the treatment or placebo group (Analysis 1.4).

We also conducted sensitivity analyses by removing two included trials (Taherian 2002; Wanchu 2001) whose allocation of concealment was unclear. The results then favoured treatment with calcium supplementation (RR 0.80, 95% CI 0.65 to 0.99; 11 trials, 15,379 women; random-effects model; Analysis 1.1). There was significant heterogeneity for this outcome ($Tau^2 = 0.04$; $Chi^2 = 20.46$, df = 9 (P = 0.02); $I^2 = 56\%$).

To investigate possible publication bias we generated a funnel plot (*see* Figure 3). Visual examination of the funnel plot suggested there might be some asymmetry and the possibility of publication bias. However, substantial heterogeneity (as is found with this outcome), reporting bias and chance can each contribute to funnel plot asymmetry (Sterne 2011). Further, there were only 13 trials included in the analysis, and for outcomes with heterogeneity the minimum of recommendation of 10 trials may not be adequate (Sterne 2011). We therefore concluded that there was no strong evidence of publication bias for the outcome of preterm birth before 37 weeks.

Figure 3. Funnel plot of comparison: 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), outcome: 1.1 Preterm birth (a) Birth prior to 37 weeks.



Infant outcomes

1. Low birthweight (less than 2500 g)

There was no statistically significant protective effect of calcium supplementation on low birthweight (six trials, Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Villar 1990; Villar 2006, with 14,162 women); (RR 0.93, 95% CI 0.81 to 1.07; random-effects model). However, there was significant heterogeneity between trials ($Tau^2 = 0.01$; $Chi^2 = 10.61$, df = 4 (P = 0.03); $I^2 = 62\%$; Analysis 2.1). Women from these trials all received a high dose.

We planned to carry out subgroup analyses for starting time and for type of calcium supplementation. There was some evidence that the starting time of supplementation was associated with different treatment effects (Test for subgroup differences: $Chi^2 = 8.77$, df = 1 (P = 0.003), $I^2 = 88.6\%$). In two studies supplementation started early and there was no evidence of a significant difference between treatment and control groups (RR 0.98, 95% CI 0.94 to 1.03; three trials, 13,425 women), whereas the treatment appeared to have a significant effect in studies where supplementation started after 20 weeks' gestation (RR 0.41, 95% CI 0.23 to 0.73; three trials, 737 women). However, as a total of only six studies contributed estimable data to this subgroup analysis, these differences may have occurred by chance (Analysis 2.2). For type of calcium supplementation, most studies (Crowther 1999; Kumar 2009; Levine 1997; Villar 1990; Villar 2006) used calcium carbonate and one trial (Lopez-Jaramillo 1989) used calcium gluconate (Analysis 2.3).

We did not conduct sensitivity analyses because all included trials for this outcome were rated as 'low risk of bias' for allocation of concealment.

We did not investigate publication bias for this outcome because the number of included trials was insufficient (six trials).

Secondary outcomes

Maternal outcomes

1. Preterm birth less than 34 weeks' gestation

There was no statistically significant difference in birth prior to 34 weeks between calcium supplementation versus placebo or no treatment (four trials, Crowther 1999; Kumar 2009; Levine 1997; Wanchu 2001, 5669 women) (RR 1.04, 95% CI 0.80 to 1.36) (Analysis 1.5). We did not perform subgroup analysis for this outcome as there was no evidence of substantial heterogeneity ($I^2 = 0\%$).

We performed a sensitivity analyses and removed one included trial (Wanchu 2001) that had 'unclear' risk of bias for allocation concealment. The result did not change (RR 1.03, 95% CI 0.79 to 1.35, three trials, 5569 women) (Analysis 1.6).

2. Maternal weight gain

Three trials (Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Villar 1987, 404 women) evaluated the effect of calcium supplementation on maternal weight gain. There was no statistically significant difference between treatment versus placebo or no treatment. We found no statistically significant difference between groups (mean difference (MD) -29.46 g per week, 95% CI -119.80 to 60.89 g per week; random-effects model) (Analysis 1.7). There was also substantial heterogeneity between trials ($Tau^2 = 5007.60$, $I^2 = 80\%$).

3. Maternal bone mineral density (BMD)

There was only one trial, involving 273 women (Raman 1978) that evaluated the effect of calcium supplementation and placebo on BMD. The author used radiographic density calculated and expressed in terms of aluminium equivalents as defined by Williams and Mason (Williams 1962).

We have presented the data for this outcome separately for treatment arms receiving different doses of supplementation.

In calcium 300 mg:

- first phalanx: there was no statistically significant difference between treatment versus placebo or no treatment (62 women, MD -0.07 g/cm^2, 95% CI -0.29 to 0.15 g/cm^2 (Analysis 1.8));
- second metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (62 women, MD 0.19 g/cm^2, 95% CI -0.02 to 0.40 g/cm^2 (Analysis 1.9));
- fourth metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (62 women, MD 0.06 g/cm^2, 95% CI -0.17 to 0.29 g/cm^2 (Analysis 1.10)).

In calcium 600 mg:

- first phalanx: there was no statistically significant difference between treatment versus placebo or no treatment (63 women, MD 0.09 g/cm^2, 95% CI -0.10 to 0.28 g/cm^2 (Analysis 1.11));
- second metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (63 women, MD 0.14 g/cm^2, 95% CI -0.11 to 0.39 g/cm^2 (Analysis 1.12));
- fourth metacarpal: there was no statistically significant difference between treatment versus placebo or no treatment (63 women, MD 0.07 g/cm^2, 95% CI -0.13 to 0.27 g/cm^2 (Analysis 1.13)).

4. Maternal death

Two trials involving 8974 women (Goldberg 2013; Villar 2006) reported this outcome. Although there appeared to be fewer deaths in the group receiving calcium supplements compared with controls (two versus seven), the difference between groups was not statistically significant (RR 0.29, 95% CI 0.06 to 1.38; Analysis 1.14).

5. Maternal admission to intensive care unit

Only one trial with 8312 women reported on this outcome (Villar 2006). There was no statistically significant difference between treatment and control groups (RR 0.84, 95% CI 0.66 to 1.07) (Analysis 1.15).

6. Mode of birth - vaginal birth, Instrumental vaginal birth, caesarean section (non-prespecified outcome)

- Vaginal birth: eight trials involving 6916 women (Belizan 1991; Crowther 1999; Levine 1997; Purwar 1996; Rogers 1999; Sanchez-Ramos 1995 ; Villar 1990; Wanchu 2001) reported on this outcome. There was no statistically significant difference between treatment and control groups (RR 1.01, 95% CI 0.99 to 1.03) (Analysis 1.16).
- Instrumental birth: two trials involving 675 women (Crowther 1999; Rogers 1999) reported on this outcome. There was no statistically significant difference between treatment and control groups (RR 0.89, 95% CI 0.66 to 1.20) (Analysis 1.17).
- Caesarean section: nine trials involving 7440 women (Belizan 1991; Crowther 1999; Kumar 2009; Levine 1997; Purwar 1996; Rogers 1999; Sanchez-Ramos 1995; Villar 1990; Wanchu 2001) reported on this outcome. There was no statistically significant difference between treatment and control groups (RR 0.99, 95% CI 0.89 to 1.10) (Analysis 1.18).

7. Postpartum haemorrhage (non-prespecified outcome)

Data were not available for this outcome.

Data were not available for the following maternal secondary outcomes: leg cramps; backache; tetany (muscle spasm and twitching); incidence of fracture; duration of breastfeeding; tremor; paraesthesia.

Fetal and neonatal outcomes

1. Perinatal mortality

Eight trials (15,785 women) reported perinatal mortality (Belizan 1991; Goldberg 2013; Levine 1997; Lopez-Jaramillo 1997; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 2006). There was no statistically significant difference between the groups (RR 0.87, 95% CI 0.72 to 1.06) (Analysis 2.5).

2. Stillbirth or fetal death

Six trials (Crowther 1999; Goldberg 2013; Kumar 2009; Levine 1997; Taherian 2002; Villar 2006) involving 15,269 women reported stillbirth or fetal death separately. There was no statistically significant difference between the groups (RR 0.91, 95% CI 0.72 to 1.14) (Analysis 2.6).

3. Neonatal death

Data were not available for this outcome.

4. Admission to neonatal intensive care unit

Admission to neonatal intensive care unit was reported in four trials involving 14,062 women (Belizan 1991; Levine 1997; Sanchez-Ramos 1994; Villar 2006). There was no statistically significant difference between the groups (RR 1.05, 95% CI 0.94 to 1.18; I^2 = 0%) (Analysis 2.7).

5. Birthweight

Mean birthweight (g) was reported in 21 trials involving 9202 women (Belizan 1983; Belizan 1991; Boggess 1997; Chan 2006; Crowther 1999; Goldberg 2013; Karandish 2003; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Lopez-Jaramillo 1997; Niromanesh 2001; Purwar 1996; Raman 1978; Rogers 1999; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1987; Villar 1990; Wanchu 2001). (In the trials by Belizan 1983 and Raman 1978 data were reported separately for women receiving different doses of calcium; in the meta-analysis we have therefore included findings for different doses separately as there was some heterogeneity between the different treatment arms; in both cases we divided the control group between the two entries to avoid double counting.) There was a statistically significant difference in birthweight between the groups (MD 56.40, 95% CI 13.55 to 99.25); Tau^2 = 5668.70, I^2 = 74%; random-effects model) (Analysis 2.4) with the women in the calcium supplementation group on average having heavier babies than those in the control group.

6. Birth length

Birth length was reported in seven trials (6389 women) (Belizan 1983; Belizan 1991; Goldberg 2013; Karandish 2003; Levine 1997; Raman 1978; Villar 1990). There was no statistically significant difference between the groups (MD -0.09, 95% CI -0.25 to 0.06) (Analysis 2.8).

7. Head circumference

Three trials involving 460 women reported head circumference (Belizan 1983; Goldberg 2013; Karandish 2003) (again data for the two treatment arms of the Belizan 1983 trial were entered separately with the control group shared between entries). There was no statistically significant difference between the groups (MD -0.09, 95% CI -0.36 to 0.18) (Analysis 2.9).

8. Intrauterine growth restriction

Intrauterine growth restriction was reported in six trials involving 1701 women (Kumar 2009; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Taherian 2002; Villar 1990). There was no statistically significant difference between the groups (RR 0.83, 95% CI 0.61 to 1.13) (Analysis 2.10).

9. Neonatal BMD

We presented the data for this outcome separately as subgroups (with subtotals only) due to the different definition of this outcome as defined by authors (Analysis 2.11):

- total body: there was no statistically significant difference between treatment versus placebo or no treatment in two trials, 300 women (Jarjou 2006; Levine 1997; MD 0.00 g/cm^2, 95% CI 0.00 to 0.01 g/cm^2; I^2 = 0%);
- midshaft radius: there was no statistically significant difference between treatment versus placebo or no treatment in one trial involving 122 women (Jarjou 2006; MD 0.00 g/cm^2, 95% CI -0.01 to 0.01 g/cm^2);
- lumbar spine 1 to 4: there was no statistically significant difference between treatment versus placebo or no treatment in one trial involving 256 women (Levine 1997; MD 0.01 g/cm^2, 95% CI 0.00 to 0.02 g/cm^2).

We have excluded the data from the Raman 1978 trial from our meta-analysis because they were skewed but they have been presented separately in an additional table (*see* Table 1).

Data were not available for the following secondary fetal and neonatal outcomes: osteopenia; rickets; fracture.

Adverse outcomes, compliance and maternal satisfaction

1. Side effects of calcium supplementation

Four trials reported side effects of calcium supplementation (Belizan 1991; Villar 1987; Villar 2006; Wanchu 2001). We have presented the data for this outcome separately as subgroups (with subtotals only) due to the different definitions of this outcome in the trials (Analysis 3.1).

- Maternal cholestatic jaundice: there was no statistically significant difference between the groups in one trial involving 100 women (Wanchu 2001) (RR 3.00, 95% CI 0.13 to 71.92).
- Gastrointestinal symptoms consisting of nausea, heartburn and diarrhoea: there was no statistically significant difference between the groups in one trial involving 52 women (Villar 1987) (RR 2.16, 95% CI 0.43 to 10.78).
- Gall stones: there was no statistically significant difference between the groups in one trial involving 518 women (Belizan 1991) (RR 1.35, 95% CI 0.48 to 3.85).
- Headache, vomiting, backache, swelling, vaginal and urinary complaints, dyspepsia, abdominal pain: there was no statistically significant difference between the groups in one trial involving 8312 women (Villar 2006) (RR 1.02, 95% CI 0.93 to 1.12).

2. Urinary stones

Three trials involving 13,419 women reported this outcome (Belizan 1991; Levine 1997; Villar 2006). There was no statistically significant difference between the groups (RR 1.11, 95% CI 0.48 to 2.54; I^2 = 39%) (Analysis 3.2).

3. Urinary tract infection

Three trials involving 1743 women reported this outcome (Belizan 1991; Crowther 1999; Villar 1990). There was no statistically significant difference between the groups (RR 0.95, 95% CI 0.69 to 1.30; I^2 = 0%) (Analysis 3.3).

5. Renal colic

This outcome was reported in one trial with 8312 women (Villar 2006). There was no evidence of a statistically significant difference between groups (RR 1.67, 95% CI 0.40 to 6.99) (Analysis 3.4).

5. Impaired renal function

There was no statistically significant difference between the groups for this outcome in one trial, involving 4589 women (Levine 1997) (RR 0.91, 95% CI 0.51 to 1.64) (Analysis 3.8) (Analysis 3.5).

6. Maternal anaemia

One trials, involving 1098 women, reported this outcome (Belizan 1991). There was no statistically significant difference between the groups (RR 1.04, 95% CI 0.9 to 1.22) (Analysis 3.6).

7. Compliance

Data were not available for this outcome.

8. Satisfaction

Data were not available for this outcome.

DISCUSSION

Summary of main results

Calcium supplementation did not reduce preterm birth. Dosage, prescription timing and the type of calcium supplementation did not effect this outcome. Calcium supplementation did not decrease the rate of low birthweight. Timing of supplementation and the type of calcium supplementation did not show any clear protective effect for low birthweight. No trial reported the effect of low-dose calcium supplementation (less than 1000 mg) on low birthweight babies. There was no evidence that calcium supplementation had any effect on maternal weight gain during pregnancy. There was no evidence to support the benefit of calcium supplementation in increasing bone mineral density in pregnant women but in infants, there was a statistically significant difference between treatment and placebo or no treatment in total body and tibial bone mineral density. While there was a statistically significant increase in birthweight in the calcium supplementation group, there was also high heterogeneity among the studies, so the results for this outcome should be interpreted with caution. Additionally, the 56 g increase in birthweight might not be clinically important. There was no evidence that calcium supplementation reduced the rate of intrauterine growth restriction, perinatal mortality, stillbirth or fetal death rate. Calcium supplementation also did not increase birth length or fetal head circumference. We found no evidence to show that calcium supplementation was associated with side effects such as postpartum haemorrhage, cholestatic jaundice, gall stones, gastrointestinal symptoms, headache, urinary stones, urinary tract infection or impaired renal function.

Overall completeness and applicability of evidence

Missing data amounted to 4.01% overall (745 in 17,842). One small trial showed a marked loss of follow-up (68.1%, Raman 1978). The loss to follow-up rates in most trials were less than 20%. Most trials prespecified outcomes in included studies especially the primary outcomes, but no data were reported for some of our secondary outcomes. As we mentioned above, the primary objectives of most of the included studies were incidence of pregnancy-induced hypertension or changes in blood pressure, which were not relevant to this review. However, these studies also had other outcomes relevant to this review, e.g. preterm birth, maternal weight gain, gestational age, birthweight, birth length and therefore, we have included them.

The largest trial in this review (Villar 2006) recruited pregnant women from a population who received less than 600 mg of dietary calcium per day. The other two big trials (Belizan 1991; Levine 1997) did not limit daily calcium intake. In addition, there were variations between trials in terms of duration of supplementation. The subgroup analysis to assess the effect on preterm delivery before 37 weeks of calcium supplementation before versus after 20 weeks' gestation revealed no protective effect on either group. There were too few studies to assess other types of calcium prescribed or other outcomes of interest such as preterm delivery before 34 weeks, maternal bone mineral density, and major fetal outcomes. This may be evidence that routine calcium supplementation in pregnant women for preventing preterm birth and low birthweight is not warranted.

The largest trial in this review (Villar 2006) recruited pregnant women from a population who received less than 600 mg of dietary calcium per day. The other two big trials (Belizan 1991; Levine 1997) did not limit daily calcium intake. In addition, there were variations between trials in terms of duration of supplementation.

The main analysis to assess the effect on preterm delivery before 37 and 34 weeks did not show significant benefit, but in a sensitivity analysis of 11 low risk of bias trials (Belizan 1991; Boggess 1997; Crowther 1999; Kumar 2009; Levine 1997; Lopez-Jaramillo 1989; Purwar 1996; Sanchez-Ramos 1994; Sanchez-Ramos 1995; Villar 1990; Villar 2006), there was a statistically significant benefit of calcium supplementation in reducing preterm delivery less than 37 weeks. Type of calcium supplementation and timing for prescribing did not make any differences.

Hofmeyr 2014 found a reduction in preterm birth for women receiving high-dose calcium supplementation (11 trials, 15,275 women; risk ratio (RR) 0.76, 95% confidence interval (CI) 0.60 to 0.97; I^2 = 60%). Hofmeyr 2014 also found a reduction in the risk of developing pre-eclampsia for women receiving supplementation (13 trials, 15,730 women; RR 0.45, 95% Cl 0.31 to 0.65; I^2 = 70%). There were eight trials in common for the preterm outcome for this and the Hofmeyr review. However, results for the preterm birth prior to 37 weeks outcome in this systematic review did not reach statistical significance until two trials were removed during sensitivity analysis (see Analysis 1.1). Inclusion criteria between the reviews differed, and therefore the results were also different.

Quality of the evidence

Most of the studies (17 of the 25 trials) were at low risk of bias for both sequence generation and allocation concealment, *see* Figure 1 and Figure 2. Seven trials did not describe the methods of sequence generation or allocation concealment clearly. Three outcomes were chosen for assessment with GRADE software for quality: low birthweight (less than 2500 g), preterm birth less than 37 weeks and preterm birth less than 34 weeks. Evidence for each outcome was considered to be of moderate quality.

Potential biases in the review process

We followed methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to try to reduce bias in the review process.

Agreements and disagreements with other studies or reviews

A Cochrane review by Hofmeyr 2014 entitled '*Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems*' showed that routine calcium supplementation during pregnancy reduced the risk of pre-eclampsia and preterm birth. As discussed above, some of our results differ from Hofmeyr 2014 due to differing inclusion criteria.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that calcium supplementation did not reduce preterm birth less than 37 weeks. There is not enough evidence to assess dosage, timing and type of calcium supplementation on pregnancy outcomes other than pregnancy-induced hypertension. The review by Hofmeyr 2014 shows a significant protective effect of calcium supplementation on pre-eclampsia/eclampsia, and reduced preterm birth but our review reveals no additional benefits of calcium supplementation. The discrepancy result might be due to inadequate sample size. Therefore, calcium supplementation during pregnancy would be primarily considered to prevent pre-eclampsia.

Implications for research

Large multicentre trials to detect the benefit of calcium supplementation on preterm birth as the primary outcome are needed to provide more solid evidence.

In addition, the results from this review found that there are a few short-term additional benefits of calcium supplementation (other than pre-eclampsia prevention) other than slight increases fetal birthweight and neonatal bone mineral density. There are limited data to assess its long-term benefits such as osteoporosis in later life. Further research might be needed to provide evidence regarding long-term benefits.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Belizan 1983

Methods	Type of study: simple randomisation into 3 groups. Method of treatment allocation: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: outpatient clinic of Guatemala Social Security Hospital. Time frame: not stated. Eligible criteria: age 20 to 35 years, single fetus, without evidence of previous pathology and certain date, not receiving any medical treatment during recruitment. Total recruited: 36 pregnant women. Treatment group 1, n = 11, treatment group 2, n = 11, placebo group, n = 14.
Interventions	• Treatment Group 1 : 1 g calcium/d. • Treatment Group 2 : 2 g calcium/d. • Compared with placebo tablets. Started treatment at 15 weeks until delivery.
Outcomes	1. BP. 2. Parathyroid hormone. 3. Calcium and magnesium level. 4. Phosphorus level. 5. Pregnancy outcomes; birthweight, birth length, head circumference.

Belizan 1983 *(Continued)*

Notes	The authors did not mention how many tablets were provided in calcium 1 g, 2 g and placebo group. Missing data = 0%. For data in Analysis 2.4 and Analysis 2.9 the placebo n was halved to enable inclusion of data for treatment groups 1 and 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After the patients volunteers to participate the trial. Simple randomisation were used to devise patient into 3 groups, receive 1, 2 g calcium comparing with placebo." Comment: method of random sequence generation was not clearly described.
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were unaware of group status. Study drug and placebo were the same size and weight and had the same organoleptic characteristics.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only 3 obstetrics and gynaecology residents were in charge of measuring BP, after standardisation with double auricular stethoscope.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were analysed. MIssing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Belizan 1991

Methods	Type of study: multicentre, double-blind, randomised controlled trial. Method of treatment allocation: randomisation was conducted at each hospital by a random-generator program. A complete set of numbered, sealed, opaque envelopes containing the randomisation codes was sent to each of 3 hospitals. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 2.3%. 27 women were lost to follow-up after randomisation (14 in the calcium group, 13 in the placebo group) but before they started treatment, and therefore were not included in the followed up analyses. Follow-up was incomplete for 52 women in the calcium group and 46 in placebo group because of change of hospital, physician or residence.
Participants	Location: the women enrolled from 3 affiliated hospitals of Centro Rosario de Estudios Perinatales, Rosario, Argentina (2 were public hospitals, the another was a private hospital). Time frame: January 1987 to September 1989.

Belizan 1991 *(Continued)*

	Eligible criteria: GA < 20 weeks and confirmed by ultrasound, nulliparous, singleton pregnancy, BP < 140/90 mmHg. No evidence of present or past disease from clinical examination or laboratory tests, not taking any medications and had normal glucose tolerance test. Exclusion criteria: gestational date estimated from LMP and ultrasonography different by more than 10 days. Total recruited: 1194 pregnant women; treatment group, n = 593, control group, n = 601. A total of 579 women in the calcium group and 588 in the placebo group were included in final analyses.
Interventions	2 g calcium/d (4 tablets/day; each calcium tablet contained 500 mg calcium carbonate and granulated starch). Compared with placebo tablet. Started treatment at 20 weeks.
Outcomes	1. BP. 2. Serum total calcium. 3. Serum magnesium. 4. Urinary calcium excretion. 5. Serum phosphate. 6. Serum uric acid. 7. Pregnancy outcomes; birthweight, birth length, preterm birth, premature rupture of membrane, diabetic mellitus, third trimester bleeding, numbers of hospital admission, perinatal death. 8. Rate of urinary tract infection. 9. Rate of maternal anaemia.
Notes	Treatment group, n = 593, control group, n = 601. For final analysis, treatment group, n = 579, 588 in placebo group but for other pregnancy outcomes other than pregnancy hypertension, n = 544 in calcium group and n = 554 in control group. Missing data 27 in 1194 = 2.3%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were randomised at each hospital by a random-generator program."
Allocation concealment (selection bias)	Low risk	Quote: "A complete set of numbered, sealed, opaque envelopes containing the randomisation codes was sent to each of three hospitals."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The calcium tablets were specially prepared by a local pharmaceutical company; the placebo tablets contained lactose and granules starch and were identical to the calcium tablets with respect to weight, size, flavour and colour. The nurses and physicians responsible for prenatal care were all unaware of the women's treatment status.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The nurses and physicians responsible for prenatal care were all unaware of the women's treatment status and were also responsible for distribution the bottle of medications, taking BP and collection of blood and urine samples at every visit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Follow-up was incomplete 52 in treatment group and 46 in placebo group because of change of hospital, physician, or residence. Nonetheless, all were included in analyses up to time when they were lost to follow-up. For the subgroup with incomplete follow-up, information about delivery was available for 17 in calcium group and 12 in placebo group." Missing data 27 in 1194 = 2.3%.

Belizan 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Boggess 1997

Methods	Type of study: double-blind randomised controlled trial. Method of treatment allocation: a computer-generated random number table was used. Using a randomisation schedule in a block of 10. All containers and tablets were prepared and dispensed by the University Drug Pharmacy. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no (23 women were randomised and 18 of them completed study). Of the 5 who did not complete the study, 3 developed preterm labour and 1 was non compliance, and 1 self-discontinued study medication due to side effects. Losses to follow-up: 5 in 23 = 21.7%.
Participants	Location: University of Washington Medical Center Women's Clinic. Time frame: not stated. Eligible criteria: age 18 to 35 years who received antenatal care. Exclusion criteria: BP > 140/90 mmHg at 24 weeks, smoking or used illicit drugs, multiple gestation, had history of cardiovascular, renal, or endocrine disorder, hypertension prior to pregnancy, or calcium supplementation. Total recruited: 23 pregnant women; calcium group, n = 12, placebo group, n = 11.
Interventions	1.5 g/d of calcium carbonate. Compared with placebo tablets. Started treatment at 28 to 31 weeks.
Outcomes	Hemodynamic function measurement.
Notes	1. GA was reported as median and range. We changed them into mean and SD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study patients were assigned in a double-blind fashion to receive orally either 1.5 element calcium as calcium carbonate or placebo daily, using a randomisation schedule in blocks of ten developed by a computer-generated random number table."
Allocation concealment (selection bias)	Low risk	Quote: "All containers and tablets were prepared and dispensed by the University Drug Pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. Quote: "Placebo tablets were same size, weight, colour, and organoleptic characteristics." All participants were blinded to intervention. All containers and tablets were prepared and dispensed by the University Drug Pharmacy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All containers and tablets were prepared and dispensed by the University Drug Pharmacy. The investigators were blinded to outcome assessment.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "Twenty-three women were randomised and 18 of them completed study. Of the five who failed to complete the study; three developed preterm

Boggess 1997 *(Continued)*

All outcomes		labour (all placebo), one was noncompliance (placebo), one discontinued due to side effects (calcium)." Missing data = 5 in 23 = 21.7%; relevant data such as preterm birth were added back into the analysis.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Chan 2006

Methods	Type of study: computer-generated randomisation. Method of treatment allocation: the pregnant women were randomly assigned to 1 of 3 groups: control, orange juice fortified with calcium, and dairy. Computer-generated randomisation was kept in envelopes. Placebo: no. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up at delivery 8.3% : in control group, missing data at delivery = 0, missed 6 months visit, n = 3 and umbilical cord not collected, n = 2. In orange juice plus calcium missing data = 3, failed to meet required 4 servings, n = 12, misses 6 month visit, n = 3,and mothers blood was not collected, n = 3 and umbilical blood was not collected, n = 3. In daily group, missing data at delivery = 3, missed at 6-month visit, n = 2, mother's blood was not collected, n = 3, and umbilical blood was not collected, n = 5.
Participants	Location: University of Utah Teen Mother and Child Program. Time frame: not stated. Eligible criteria: healthy adolescent (15 to 17 years old) pregnant women. GA < 20 weeks by last normal menstrual period. Exclusion criteria: hypertension, diabetes, renal or liver diseases, used alcohol, tobacco or medications that would effect Ca metabolism during pregnancy. Total recruited: 72 healthy pregnant adolescents.
Interventions	There were 3 groups. Group 1; control (consumed usual diet) n = 23. Group 2; orange juice fortified with calcium consumed at least 4 servings of orange juice plus calcium (more than 1200 mg Ca) n = 24. Group 3; dairy (consumed at least 4 servings of dairy product (Ca more than 1200 mg) e.g., milk, yogurt, cheese, n = 25. Started treatment at 20 weeks.
Outcomes	1. Maternal weight gain, BP. 2. Newborn birthweight, lean and fat mass of infant, total body calcium.
Notes	Missing data at delivery 6 in 72 = 8.3%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Pregnant mothers were randomly assigned to one of three groups; control, orange juice fortified with calcium, and dairy. Computer-generated randomisation was kept in sealed envelopes."
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated randomisation was kept in sealed envelopes."

Chan 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The control group consumed their usual diet while the orange juice plus calcium group were counselled to consume at least four servings of orange juice plus calcium (more than 1200 mg Ca) so that their Ca intake would be similar to the dairy group.The dairy group was counselled to consume at least four servings of dairy products (more than 1200 mg Ca) daily. Dairy products consisted of milk, yogurt, and cheese." Comment: it was impossible to blind because of the different kinds of food.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Could not blind participants and investigators due to different intervention.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the authors displayed a flow chart of participants. Missing data in control group = 13%, in orange juice plus calcium = 12.5 %, in daily product 8%. Missing data at delivery 6 in 72 = 8.3%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Crowther 1999

Methods	Type of study: placebo-controlled double-blind trial. Method of treatment allocation: the randomisation schedule was prepared by the drug company with stratification made by centre using variable blocks. Placebo: yes, starch tablets. Sample size calculation: a study of 948 women was estimated to have an 80% probability of detecting differences in the rate of preterm birth at P = 0.05 and an 88% power to detect a 50% difference with the rate of PIH with the same significance level. Intention-to-treat analyses: yes. Pre-calculation samples needed 948 women to be recruited in trial but because of shortage of funds, but only 456 pregnant women were recruited. Losses to follow-up: 0%.
Participants	Location: 5 Australian Medical Centres. Time frame: August 1992 to December 1996. Eligible criteria: nulliparous, singleton pregnancy, at less than 24 weeks, with normal BP at trial entry (< 140/90 mmHg) and expected to birth at 5 collaborating centres were expected for trial but recruitment to the trial was stopped by the steering group without knowledge of study outcomes after 456 women were randomised when the limited financial resources available for the trial were exhausted. Exclusion criteria: used of antihypertensive or medical disorder where calcium supplementation was contraindicated such as renal failure, hyperparathyroidism or renal calculi. Total recruitments: 948 pregnant women planned to be recruited. Data were analysed when pregnancy outcome data were available for all 456 women recruited. Of 456, 227 were assigned to calcium group, 229 were in placebo group.
Interventions	Women were asked to take 3 tablets daily orally, equivalent 1.8 g calcium or placebo (calcium carbonate, 600 mg of elemental calcium per tablet). Started treatment at 20 weeks until delivery. Compared with 3 tablets of placebo tablets.
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; preterm birth, premature rupture of membrane, birthweight.

Crowther 1999 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was prepared by the drug company with stratification made by centre using variable blocks."
Allocation concealment (selection bias)	Low risk	Quote: "A study number was given by the central randomisation office. This corresponded to a sealed treatment pack held at the collaboration centre and were provided by Lederle Laboratories."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Women who gave consent were enrolled into the trial by telephoning the central randomization number in the Maternal Perinatal Clinic Trial Unit . The randomization schedule was prepared by the drug company with stratification made by center using variable blocks." All women and staff were blind to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Women received antenatal care and postnatal care from attending obstetrics care. Data were collected from case notes by research assistants and checked by senior obstetrician, all blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "948 women were expected for trial but recruitment to the trial was stopped by the steering group without knowledge of study outcomes after 456 women were randomised when the limitation financial resource available for the trial were exhaust. Data were performing when pregnancy outcome data were available for all 456 women recruited. Of 456: 227 were assigned to calcium group, 229 were placebo group." Comment: the number of participants in treatment and control groups was equal. Missing data = 0%.
Selective reporting (reporting bias)	High risk	Trial stopped before enrolment complete due to a shortage of research funds.
Other bias	Low risk	None identified.

Ettinger 2009

Methods	Type of study: Double-blind, randomised, placebo-controlled trial. Method of treatment allocation:not stated Placebo: yes Intention-to-treat basis: yes
Participants	Location: Mexican Social Security Institute, Mexico city, Mexico. Time frame: 2001-2003 670 women were randomised in the first trimester of pregnancy. 334 to the treatment group, and 336 to the placebo group.

Ettinger 2009 *(Continued)*

Interventions	1200 mg calcium daily (two 600-mg calcium carbonate tablets) versus placebo.
Outcomes	Maternal blood lead levels at first, second, and third trimester.
Notes	We have not included outcome data from this study as the trial specifically focused on the effects of calcium supplementation on blood lead levels. The study does not address any of the review's primary or secondary outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women were randomly assigned to received 1200 mg calcium (2 tabs of 600 mg calcium carbonate tablets) or placebo. Study described as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled trial. Study described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	670 randomised. 565 women completed follow-up. 557 included in the analysis (83%). Lost to follow-up in placebo 18%, calcium group 14%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Goldberg 2013

Methods	Type of study: double-blind, randomised, parallel, placebo-controlled trial. Method of treatment allocation: stratified by clinic to receive calcium supplementation or placebo. The assignment within each stratum was by random permuted block of 4 in each week each clinic. The allocation sequence was generated by using random-number tables. The code was held by a member of the trial team who was not directly involve in data collection and had no contact with participant. Placebo: yes, starch tablets. Sample size calculation: at 5% significance and 80% power, a sample size needed 260 participants per group. Loss to follow-up: 330 randomised to intervention and 332 to the control group. Data for 260 women in the intervention group and 265 in the control group at delivery. Attrition accounted for in study flowchart with numbers given for maternal (2), fetal (10), neonatal or infant death (25); exclusion after randomisation for incorrect GA (70) or multiple pregnancy (11) missing data for BP at 36 weeks' gestation (1) and women moving away or withdrawal (18). ITT and per protocol analyses undertaken. 3 women unaccounted for in flowchart.

Goldberg 2013 *(Continued)*

	Jarjou 2006 presents data for a subset of the women in reported in Goldberg 2013, for the outcome of neonatal bone density.
Participants	Location: 3 antenatal clinics, covering cluster of villages in different geographic regions in West Kiangin Gambia. Time frame: May 1995 - March 2000. Eligible criteria: healthy pregnant women with no medical history affecting calcium metabolism presenting for prenatal care at 1 of 3 outpatient clinics. Singleton only, gestation 18-22 weeks. Exclusion criteria: any complications of pregnancy. Total recruitments: 662 pregnant women were recruited, 330 in treatment group, 332 in placebo group. Data for 525, with loss to groups comparable.
Interventions	1500 mg calcium (3 chewable calcium carbonate tablets, each consist of 500 mg elemental calcium) versus 3 chewable placebo in similar shape, colour, and taste, from 20 weeks' gestation until delivery.
Outcomes	BP at 36 weeks' gestation. Maternal BP in first year postpartum. Infant growth measures collected at 2, 13 and 52 weeks. Breast milk calcium concentration, neonatal bone mineral density at age ≤ 1 year.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blind, randomised, parallel, placebo-controlled trial.The assignment within each stratum was by random permuted block of 4 in each week at each clinic. The allocation sequence was generated by using random-number tables.
Allocation concealment (selection bias)	Low risk	The allocation sequence was generated by using random-number tables.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment group and placebo group received identical tablets.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	BP, anthropometric measurements were measured by trained field staff using a standard protocol.
Incomplete outcome data (attrition bias) All outcomes	High risk	330 randomised to intervention and 332 to the control group. Data for 260 women in the intervention group and 265 in the control group at delivery. Attrition in both arms approximately 20%. Authors accounted for women lost in flowchart and conducted ITT analysis where possible. For infant outcomes, the denominator varies. Many infants without data for birth measurements because their mothers spent the traditional 8-day confinement period away from their village.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes are reported.
Other bias	Low risk	None detected.

Herrera 2006

Methods	Randomised controlled trial. Study described as placebo-controlled and double-blind.
Participants	Location: 3 clinical settings in Santander de Quilichao and Cali, Columbia. Healthy pregnant adolescent women < 19 yrs, between 17 and 19 weeks pregnant. Primigravidas only. No medical complications at trial entry. Women were recruited from clinics while attending outpatient prenatal care. Sample size calculation determined 26 women needed per group. 52 women randomised; data for 48. 2 women from each arm lost to follow-up.
Interventions	Oral calcium 600 mg (1 capsule twice daily) versus oral placebo 600 mg (twice daily).
Outcomes	Concentrations of plasma ionised calcium and concentration of the free intracellular calcium concentration only.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence. Randomisation for all 3 sites conducted centrally.
Allocation concealment (selection bias)	Low risk	Randomisation conducted centrally. Allocation concealed in sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and staff were unaware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff blind to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (8.4%) women lost to follow-up in each treatment group. Authors state that these exclusions did not modify the results.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes are reported.
Other bias	Low risk	None detected.

Jarjou 2006

Methods	This study reports on a subset of women. The entire sample is reported in Goldberg 2013 above. Jarjou 2006 and Goldberg 2013 do not report the same outcomes, so there is no duplication of participants in this review's analysis. Type of study: a randomised, double-blind, placebo-controlled study. Method of treatment allocation: participants were randomly assigned in double-blind fashion to receive calcium or placebo by using block of 4 from published sets of tables in each month and thereby to

Jarjou 2006 *(Continued)*

	minimise the potential for seasonal confounding. The code was held by a member of study team who was not directly involved with the collection of data in the field or laboratory and who had no contact with the study participants. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no, final analyses were 61 from 77 in treatment group, 64 from 78 in control group. Losses to follow-up: 19.3 % (30 in 155).
Participants	Location: Gambian women, in rural village of Keneba and Manduar, in the province of West King. Time frame: May 1995 to June 1999. Eligible criteria: nulliparity with no history of any medical condition known to affect calcium or bone metabolism, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation and intended to undergo delivery at the same institution, normal glucose tolerance test and willing to participate in trial, first antenatal visit BP below 140/90 mmHg and free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests. Exclusion criteria: had history or evidence of renal disease, collagen vascular disease, chronic hypertension and endocrinological disease or if they took any medication. Total recruited: 155 pregnant women. Treatment group, n = 77 and control group, n = 78 women. In the final analysis only 125 mother-infant pairs were analysed (61 in the treatment group, 64 in the control group).
Interventions	1500 mg of calcium (3 chewable tablets of calcium carbonate per day, 500 mg of elemental calcium). 3 tablets of placebo (contained microcrystalline cellulose and lactose) per day, same shape, taste and texture. The study started from 20 weeks until delivery.
Outcomes	1. Anthropometric measurement (weight, height of pregnant women and fetal birthweight, height, crown-heel, head circumference) in 24 hours postpartum. 2. Infant bone mineral density.
Notes	Lost to follow-up of infants outcomes: 16 in treatment group; only 61 infants were analysed, 14 in control group; only 64 infants were analysed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned in double-blind fashion to receive calcium or placebo by using block of 4 to ensure that equal numbers of subjects were allocated to supplement and placebo groups in each month and thereby to minimize the potential for seasonal confounding. Randomization was achieved by using published sets of tables."
Allocation concealment (selection bias)	Low risk	Quote: "The code was held by a member of study team who was not directly involved with the collection of data in the field or laboratory and who had no contact with the study participants."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects were randomly assigned in double-blind fashion to receive calcium or placebo by using block of 4. Treatment drug and placebo (contained microcrystalline cellulose and lactose) per day, same shape, taste and texture)." Women and staff blind to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The code was held by a member of study team who was not directly involved with the collection of data in the field or laboratory and who had no contact with the study participants." Anthropometric measurements collected by medical staff. Breast-milk calcium and phosphorus was collected and sent

Jarjou 2006 *(Continued)*

		to laboratory centre. Maternal urine calcium also sent to central laboratory. Matenal calcium intake assessed by field workers.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "There were no significant differences between the 2 groups in supplementation period, or compliance." Flowchart reports attrition due to maternal (1), fetal or neonatal death (5), multiple pregnancy (4), miscalculation of gestation at trial entrance (19) and lost contact (1). Missing data 30 in 155 = 19.3%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Karandish 2003

Methods	Type of study: double-blind, placebo-controlled, randomised clinical trial. Method of treatment allocation: no data. Placebo: yes (starch tablets). Intention-to-treat analyses: no, the initial number of participants were 77 pregnant women but by the end of study 68 participants remained. Losses to follow-up: 11.7 % (9 in 77).
Participants	Location: 2 prenatal clinics in county of Ahvaz, Iran. Time frame: no data. Eligible criteria: pregnant women between the ages of 18 to 35. Pregnant women in their third trimester before week 28 of their pregnancies. No history of abortion or stillbirth. Not suffering from any metabolic or chronic diseases. Not having previous history of giving birth to twins. Not being on any other supplements with the exception of iron and folic acid. Total recruited 77 pregnant women, treatment group, n = 33, placebo group, n = 35.
Interventions	1000 mg of calcium (2 capsules of 500 mg calcium carbonate) compared with placebo. The study started from 28th-30th week gestation until delivery.
Outcomes	Anthropometric parameters of neonates including weight, head circumference and length.
Notes	This paper was written in Farsi. Dr Reza Navaei kindly translated it to English using the Cochrane Pregnancy and Childbirth Group's translation form.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Double-blind, placebo-controlled, randomised clinical trial were mentioned but there was no detail of sequencing generation.

Karandish 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No detail in allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomised controlled trial. Placebo made by Manufacturer as the calcium capsules. Blinding of participants and staff.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double blind. Patients and clinic staff were unaware of type of medicine.
Incomplete outcome data (attrition bias) All outcomes	High risk	The initial participants were 77 pregnant women but the final analyses were 68 women. No details about 9 women who dropped out from the study.
Selective reporting (reporting bias)	Low risk	The preplanned outcomes were reported.
Other bias	Low risk	None identified.

Kumar 2009

Methods	Type of study: double-blinded randomised trial with simple randomisation sequence developed manually. The blinding of study participants and investigators was done by assigning coded numbers to the package. Method of treatment allocation: the packages were distributed to the participants using the random number in sequence. Placebo: yes. Intention-to-treat analyses: no, only participants 524 who delivered in hospital. Losses to follow-up: 28 from 552 = 5.1% (17 in treatment group and 11 in placebo group).
Participants	Location: At Lok Nayak Hospital, New Delhi, India. Time frame: January 2005 and December 2007. Eligible criteria: healthy normotensive primigravidas with non complicated singleton pregnancy, 12-25 weeks' gestation Exclusion criteria: multiple pregnancy, polyhydramnios, fetal malformation, diabetes, chronic hypertension, renal disease, cardiovascular disease, urolithiasis or BP > 140/90 mmHg. Total recruited 552 pregnant women, treatment group, n = 290, placebo group, n = 262.
Interventions	Oral calcium carbonate 4 tablets daily (500 mg each) compared with placebo, 4 tablets daily, from GA 12-25 week until delivery.
Outcomes	1. BP. 2. Maternal and neonatal outcomes including: pre-eclampsia, preterm delivery, induction of labour, CS, fetal distress during labour, meconium during labour, GA at delivery, gestational duration at delivery (wk; < 32, 32 to 36, 37 to 40, > 40), birthweight g, birthweight (kg < 2, 2 to 2.5, 2.5 to 4), small-for-gestational age, stillbirth.

Kumar 2009 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Double-blinded randomised trial with simple randomisation sequence developed manually.
Allocation concealment (selection bias)	Low risk	Allocation concealed by assigning treatment packages with code, which was unbroken until the end of the study. The packages were distributed to the participants using the random number in sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The blinding of study participants and investigators was done by assigning coded numbers to the package.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All women were followed up in prenatal clinic in a routine manner.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 28 from 552 = 5.1% (17 in treatment group and 11 in placebo group).
Selective reporting (reporting bias)	Low risk	The preplanned outcomes were reported.
Other bias	Low risk	None identified.

Levine 1997

Methods	Type of study: double-blind, computer-generated simple randomisation sequence. Method of treatment allocation: packages of study tablets were prepared and numbered by manufacturer and then shipped to the medical centre. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 253 in 4589 women (5.5%); 132 in the calcium group, 121 in the placebo group.
Participants	Location: The Calcium for Preeclampsia Prevention (CPEP) Trial at 5 U.S medical centres. Time frame: not stated. Eligibility criteria: nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 11 to 21 weeks of gestation and intended to undergo delivery at the same institution, normal glucose tolerance test and willing to participate in trial, BP below 134/84 mmHg and free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests. Exclusion criteria: taking medication, had bad obstetrical conditions, pre-existing disease, elevated serum concentration of creatinine (≥ 1.0 mg/dL) or calcium (≥ 10.6 mg /dlL, pregnant women with renal disease, haematuria, or history of urolithiasis in themselves or in first-degree relative and who report frequently use of calcium supplementation or antacid.

Levine 1997 *(Continued)*

	Total recruited: 4589 pregnant women; treatment group n = 2295, control group n = 2294.
Interventions	2 g of calcium (4 chewable tablets of calcium carbonate per day, 500 mg of elemental calcium), start at 13 to 20 weeks until delivery, 2 tablets with morning meal and 2 tablets with evening meal. Compared with 4 tablets of placebo (contained lactose and granulated starch) per day, same size, weight and colour.
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; preterm birth, premature rupture of membrane, birthweight, birth length, admission to NICU, perinatal losses. 3. Urolithiasis, renal insufficiency.
Notes	Koo 1999 was another subset report of Levine 1997. Total recruited: 289 pregnant women. 13 refused consent; only 256 women and 256 infants were included (128 in each group). 1. Fetal bone mineral density, bone mineral content. 2. Pregnancy outcomes; GA, birthweight, birth length, and head circumference.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Package of study tablets were prepared and numbered by manufacturer according to a computer-generated simple randomisation sequence developed by statisticians."
Allocation concealment (selection bias)	Low risk	Quote: "Package of study tablets were prepared and numbered by manufacturer according to a computer-generated simple randomisation sequence developed by statisticians and then were shipped to the medical centres. Upon enrolment, each woman was assigned the next number packages of medication at the centre and thus was randomised automatically to receive calcium or placebo according to the pre assigned random sequence."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, calcium supplementation versus placebo. Package of study tablets were prepared and numbered by manufacturer according to a computer-generated simple randomisation sequence developed by statisticians. Women and staff blind to allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All pregnant women received routines prenatal care. Staff blind to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 4589 women enrolled in the study, 253 women (5.5%) were lost to follow-up; 132 in the calcium group, 121 in the placebo group." Missing data 253 in 4589 = 5.5%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Lopez-Jaramillo 1989

Methods	Type of study: prospective, randomised, double-blind, controlled clinical trial.

Lopez-Jaramillo 1989 *(Continued)*

	Method of treatment allocation: table of random numbers. The containers and the calcium tablets for both groups were prepared in Facultad de Quimica y Farmacia. Stratification: not stated. Placebo: yes, start tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 13.2%. Only women with no missing values for any of the covariate and outcome variables were included in the analysis. 49 in calcium group and 43 in placebo group. 6 women in calcium group and 8 in placebo group were eliminated from analysis because they were delivered before 38 weeks.
Participants	Location: antenatal outpatient clinic in the Hospital Gineco-Obsterica Isdro Aroya in Quito, Ecuador. Time frame: 30 months during 1984-1986. Eligible criteria: nulliparity, age ≤ 25 years, certain LMP, registration at antenatal clinic for the first prenatal visit before 24 weeks' gestation and residency in Quito (2800 m altitude) for a period of at least 1 year before conception, BP < 120/80 mmHg and free for of any underlying medical disorders based on a comprehensive medical student examination and routine laboratory tests. Exclusion criteria: had history of cardiovascular, renal or endocrinological disease or if they took any type of drug or vitamin/mineral preparation. Total recruited: 106 pregnant women; n = 55 in treatment group, n = 51 in control group.
Interventions	2000 mg of calcium (4 tablets of calcium gluconate daily, 500 mg of elemental calcium) compared with 4 tablets of placebo per day, same size, weight and colour. Started treatment at 23 weeks until delivery.
Outcomes	1. BP develop PIH. 2. Pregnancy outcomes; weight gain, preterm birth, birthweight, perinatal mortality. 3. Serum ionised calcium concentrations.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a table of random numbers each patients was assigned independently in sequence to one of two treatment regimens."
Allocation concealment (selection bias)	Low risk	Quote: "The containers and the calcium tablets for both groups were prepared in Facultad de Quimica y Farmacia."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The placebo group also received 4 tablets daily of the same size, weight, colour and organoleptic characteristics as calcium tablets.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "106 women satisfactory met the subject selection criteria. Only women with no missing values for any of the covariate and outcome variables were included in these statistical analysis. 49 in the calcium supplemented group and 43 in the placebo group. Six women in calcium supplement group

Lopez-Jaramillo 1989 *(Continued)*

		and eight in the placebo group were eliminated from analysis because they were delivery before 38 weeks." Missing data 14 in 106 = 13.2%.
Selective reporting (reporting bias)	Unclear risk	Comment: not all enrolled participants were analysed.
Other bias	Low risk	None identified.

Lopez-Jaramillo 1997

Methods	Type of study: a prospective, randomised, double-blind, controlled clinical trial. Sequence according to random numbers table. Method of treatment allocation: used a table of random numbers to assign each patient independently in sequence to 1 of 2 treatment regimens. Treatment assignment was double-blind, with composition of tablets unknown to the patients and to all clinical personnel involved in the study. The containers and tablets were prepared in the Facultad de Quimica y Farmacia, Universidad Central del Ecuador. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: yes, 14 in 274 = 5.1%.
Participants	Location: Hospital Gineco-Obstetrico Isidro Ayora in Quito, Ecuador. Time frame: 56-month period between 1990 to 1995. Eligible criteria: age < 17.5 years, nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation, residency in Quito (2800 m altitude) for a period of at least 1 year before conception, BP < 120/80 mmHg and free from any underlying medical disorders, based on a comprehensive medical examination and laboratory test. Exclusion criteria: had history of cardiovascular, renal or endocrinological disease or if they took any type of drugs or vitamin/mineral preparations. Total recruited: 274 pregnant teenagers were randomised; 14 women failed to complete the protocol (3 changed residence, 7 changed to a private hospital, 2 changed to hospital of social insurance, 2 by noncompliance to treatment); only 260 completed the study, 125 girls received 2000 mg calcium, 135 girls in control group.
Interventions	2 g calcium (4 tablets of calcium carbonate per day, 500 mg of elemental calcium) compared with 4 tablets of placebo (contained lactose and granulated starch) per day, same size, weight, colour and organoleptic characteristics as calcium tablets.
Outcomes	1. Incidence of PIH. 2. Serum ionised calcium concentrations. 3. Pregnancy outcomes; GA, weight gain, birthweight, fetal mortality. 4. Side effects of calcium.
Notes	
Risk of bias	

Lopez-Jaramillo 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a table of random numbers to assigned each patient independently in sequence to one of two treatment regimens."
Allocation concealment (selection bias)	Low risk	Quote: "The containers and tablets were prepared in the Facultad de Quimica y Farmacia,Universidad Central del Ecuador."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "We used a table of random numbers to assigned each patient independently in sequence to one of two treatment regimens." Quote: "Treatment assignment was double-blind, with the composition of the tablets unknown to the patients and to all clinical personnel involve in the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Treatment assignment was double-blind, with the composition of the tablets unknown to the patients and to all clinical personnel involve in the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "274 teenagers were randomised and then 14 women failed to completed the protocol (3 changed the residence, 7 changed to the private hospital, 2 changed to hospital of social insurance, 2 by non-compliance to treatment) then only 260 completed the study; 125 girls received 2000 mg calcium, 135 girls in the control group." Missing data 5.1%. The authors did not provide information about how many people were missing in each group.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Niromanesh 2001

Methods	Type of study: double-blind, placebo-controlled clinical trial. Randomly assigned to 1 of 2 treatments. Method of treatment allocation: the manufacturing company coded the tablets. The hospital pharmacy dispensed the tablet among the participants. Stratification: not stated. Placebo: yes, starch tablet. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: Mirza-Kochak-Khan Gynecology Hospital, Tehran, Iran. Time frame: not stated. Eligible criteria: high risk for pre-eclampsia, positive roll-over test, GA 28 to 32 weeks, BP < 140/90 mmHg. Exclusion criteria: negative for roll-over test and had any chronic condition such as diabetes, renal diseases, cardiovascular disease, hypertension, and severe anaemia. Total recruited: 30 women at high risk of pre-eclampsia (15 in the calcium group, 15 in the control group).
Interventions	2 g of calcium (4 tablets of 500 mg orally every 6 hours). Compared with placebo. Started treatment at 28 to 32 weeks.

Niromanesh 2001 *(Continued)*

Outcomes	1. Incidence of PIH. 2. Maternal weight gain. 3. Pregnancy outcomes; duration of pregnancy, birthweight.
Notes	No details about the type of calcium.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Thirty women at high risk of preeclampsia were randomly assigned to 2 g of calcium daily intake and placebo regimen." Comment: the method of sequence generation was not described.
Allocation concealment (selection bias)	Low risk	Quote: "The manufactory company coded the tablets. The hospital pharmacy dispensed the tablet among the subjects."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:" Randomization and blinding of subjects and investigator were managed by providing coded tablets of the same packaging and physical characteristics for both calcium and placebo tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:" Randomization and blinding of subjects and investigator were managed by providing coded tablets of the same packaging and physical characteristics for both calcium and placebo tablets." Blood pressure and proteinuria were evaluated in each visit.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There was no loss to follow up in the course of study." Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Purwar 1996

Methods	Type of study: randomised double-blind placebo-controlled trial. Method of treatment allocation: the women were assigned randomly in a double-blind fashion to 1 of 2 treatment groups (calcium/placebo) using computer-generated random number table. All the containers and tablets were specially prepared by local Universal pharmaceutical, Nagpur. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: yes, 11 in 201 = 5.5%.
Participants	Location: the Government Medical College and Hospital, Nagpur, India. Time frame: October 1,1993 to December 31, 1994. Eligible criteria: nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation and intending to undergo delivery at the

Purwar 1996 *(Continued)*

	same institution, normal glucose tolerance test < 140 mg/dl and willing to participate in trial, first antenatal visit below 140/90 mmHg and free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests. Exclusion criteria: renal disease, collagen vascular disease, chronic hypertension, endocrinological disease or if on any medication. Total recruited: 201 pregnant women; treatment group, n = 103, control group, n = 98. Final number for analysis (treatment group n = 97, control group n = 93).
Interventions	2 g calcium (4 tablets of 500 mg calcium carbonate). Placebo (4 tablets of placebo) same size, weight and colour.
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; preterm birth, birthweight, fetal growth restriction.
Notes	Missing data 11 in 201 = 5.5%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The women were assigned randomly in a double-blind fashion at 20 weeks gestation to 1 of 2 treatment groups (calcium/placebo) using computer-generated random number table."
Allocation concealment (selection bias)	Low risk	Quote: "All the containers and tablets used were specially prepared for the study by local Universal Pharmaceutical Pvt Ltd, Nagpur."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The calcium supplemented group received 4 tablets of calcium (500 mg of elemental calcium each) for total 2 g and the placebo group received 4 tablets of the same size, weight, and colour."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blood pressure were measured by one physician specially trained. Any ante/intrapartum maternal and fetal complications were recorded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 98 women randomly assigned to the placebo groups and 103 in calcium groups. Eleven women (5.47%) were lost to follow-up after randomisation (5 in the placebo group and 6 in the calcium group). The total of 93 women in the placebo group and 98 women in the calcium group were included in the fin final analysis." Missing data 11 in 201 = 5.5%.
Selective reporting (reporting bias)	Unclear risk	None identified. There were inconsistent missing data. The number lost to follow-up is 11 from 201; t200 participants should have remained in the final analysis, but the given number included in final analysis was 201 participants.
Other bias	Low risk	None identified.

Raman 1978

Methods	Type of study: pregnant women were assigned by strict rotation to 1 of 3 groups.

Raman 1978 *(Continued)*

	Method of treatment allocation: not clearly stated. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: 186 in 273 = 68.1%.
Participants	Location: India, poor segment of the population. Time frame: not stated. Eligible criteria: pregnant women who were in low-economic status and had regularly consumed supplements were enrolled. Exclusion criteria: pregnant women suffered from complications such as toxaemia, hypertension and diabetes. Total recruited: 273 pregnant women divided into 3 groups.
Interventions	Calcium lactate was given in tablet form supplying 150 mg of elemental calcium per tablet. Started treatment at 18 to 22 weeks until delivery. Group 1: control, n = 38 no treatment. Group 2: n = 25 received calcium 300 mg/d. Group 3: n = 24 received calcium 600 mg /d.
Outcomes	1. X-ray left hand (anteroposterior view) of mothers. 2. X-ray ulna, radius, tibia fibular of neonate. 3. Densitometry of metacarpal and 4-1 phalangeal of mothers. 4. Densitometry of ulna, radius, tibia fibular of neonate.
Notes	Comment: only 87 participants completed data: 38, 25, 24 participants in 3 groups respectively, high rate of losses to follow-up 186 in 273 = 68.1%. For data in Analysis 2.4 the placebo n was halved to enable inclusion of data for treatment groups 1 and 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the women were assigned by strictly rotation to one of three groups". Comment: method of sequence generation was not stated.
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment versus no treatment. The participants were not blinded. The intervention was divided into 2 groups which unequal dosage.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unable to blind outcomes assessment due to different dosage and treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 273 mothers registered, data completed in all aspect, could be obtained in 87 subjects (38, 25, 24 respectively)". Comment: high rate of loss to follow-up.

Raman 1978 *(Continued)*

		Missing data 186 in 273 = 68.1%. (in treatment group (calcium 300 mg/d) = 72.5%; in treatment group (calcium 600 mg/d) = 73.6%; in control group = 58.2%).
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Low risk	None identified.

Rogers 1999

Methods	Type of study: randomised trial. Method of treatment allocation: unsealed envelopes. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 18 in 237 =7.6%.
Participants	Location: Chinese Women's Hospital, Hong Kong. Time frame: July 1992 to December 1994. Eligible criteria: normotensive, MAP > 80 and < 106 mmHg, second trimester, singleton and used cutoff value 60 mmHg of left lateral position. Exclusion criteria: MAP < 60 mmHg. Total recruited: 500 pregnant women (131 patients were excluded only 369 patients were randomised),154 in calcium group, 132 in low-dose aspirin, 83 in control group.
Interventions	Compared 3 groups of total 369 patients. 1. Calcium (154 patients) 600 mg/day from 22 to 32 weeks and 1200 mg/d in dividing dose from 32 weeks to delivery. 2. Low dose aspirin (132 patients) 80 mg/d starting at 22 weeks until delivery. 3. Control group were no treatment in 83 patients.
Outcomes	1. Mean arterial BP. 2. Pregnancy outcomes; GA, birthweight, Apgar score. 3. Incidence of proteinurics and non proteinurics PIH.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was into three groups: control, low-dose aspirin, and calcium supplementation in a ratio of 1:2:2 using five unsealed envelopes." Of 500 nulliparous women screened, 369 were randomised; 154 were in calcium group, 132 were in low-dose aspirin and 83 as control group."
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was into three groups; control, low-dose aspirin, and calcium supplementation in a ratio of 1:2:2 using five unsealed envelopes."

Rogers 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants received different interventions. Could not blind both participants and assessors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All randomisation, data collection and data entry were undertaken by the same research assistant with the exception of outcome data, which were entered by the first two authors. The research assistant was therefore blind to the outcome group." It is unclear whether the authors collecting data would have been aware of group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty (10%) patients eventually delivered in other hospitals and were therefore not subjected to analysis, as they could not reliably be classified into the 3 outcomes groups. 144, 118, and 75 were in calcium group, low-dose aspirin, and control groups respectively were included in final analysis." Missing data 18 in 237 = 7.6%.
Selective reporting (reporting bias)	Unclear risk	None identified.
Other bias	Low risk	None identified.

Sanchez-Ramos 1994

Methods	Type of study: randomised double-blind, placebo-controlled clinical trial. Method of treatment allocation: women with positive angiotensin test were randomised by means of a computer-generated list. Calcium and placebo tablets were provided by pharmaceutical company. Stratification: not stated. Placebo: yes, placebo. Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: 4 in 67 = 6.0%. Post randomised exclusion: 6 in 67 = 8.9 % did not comply fully with the protocol; 4 were excluded from analysis after randomisation because of a lack of information, 1 was admitted to another hospital (in placebo group), another woman refused to participate after 1 week of trial (in calcium group).
Participants	Location: University of Florida Health Science Center, Jacksonville, Florida. Time frame: January 1, 1989 to July 30, 1993. Eligible criteria: normotensive, nulliparous with increased risk of PIH with positive angiotensin sensitivity test only who were positive roll-over test (women supine diastolic BP value were more than 20 mmHg higher than those obtained on her side) received angiotensin infusion at 24 to 28 weeks. Exclusion criteria: participants with conditions known to increase the incidence of PIH, including history or evidence of renal disease, collagen vascular disease, diabetes mellitus, chronic hypertension and multiple pregnancy. Total recruited: 281 pregnant women were positive roll-over test; 67 women positive angiotensin sensitivity test; 33 received calcium, 34 received placebo. Final analyses, calcium group, n = 29, control group, n = 34.
Interventions	2 g of calcium carbonate, compared with placebo (contained starch and were identical to calcium tablets with respected to weight, size, flavour and appearance).
Outcomes	1. Incidence PIH.

Sanchez-Ramos 1994 *(Continued)*

2. Pregnancy outcomes; GA, preterm birth, birthweight, Apgar score, NICU admission, fetal growth restriction, perinatal death.

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Women with positive angiotensin test were randomised by means of a computer-generated list to receive either 2 g/day of elemental calcium or matching placebo."
Allocation concealment (selection bias)	Low risk	Quote: "Calcium and placebo tablets were provided by pharmaceutical company."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to intervention. Placebo contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were blinded to treatment. Placebo tablets contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Six women (8.9%) did not comply fully the protocol; of these, four were excluded from analysis after randomisation because lack of information. One had a single follow-up prenatal visited and refused to continue participating in the study. She was admitted to another hospital at 35 weeks' gestation with severe preeclampsia and required labour induction (in placebo group). Another woman refused to participate after one week of trial (in calcium group)." Missing data 4 in 67 = 6%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Sanchez-Ramos 1995

Methods	Type of study: computer-generated list of random numbers. Method of treatment allocation: the randomisation list was maintain by pharmaceutical personnel. The drug and placebo were delivered by pharmacy to antepartum ward, where a nurse administered the medication. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: no, because of a decline in perinatal research support, the study was terminated 3 cases earlier than suggested by power analysis. Losses to follow-up: 0%.
Participants	Location: University Medical Center, Jacksonville, Florida, USA.

Sanchez-Ramos 1995 *(Continued)*

	Time frame: July 1990 - January 1993. Eligible criteria: nulliparity, 24 to 36 weeks' gestation, mild pre-eclampsia and no evidence of severe pre-eclampsia within 48 hours of admission. Exclusion criteria: proteinuria ≥ 5 g/d, platelet count < 100,000, oliguria (urine < 500 mL/d), pulmonary oedema, elevated liver enzyme > 200 U/L, microangiopathic haemodynamic anaemia, fetal growth retardation, known sensitivity to calcium, chronic hypertension, chronic renal disease, diabetes mellitus,or calcium supplement before admission. Total recruited: 75 eligible participants; 36 in treatment group, 39 in control group (because of a decline in perinatal research support, the study was terminated 3 cases earlier than suggested by power analysis).
Interventions	2 g of calcium/d (4 tablets of calcium carbonate per day, 500 mg of elemental calcium). Placebo (4 tablets of placebo per day, same size, weight and colour).
Outcomes	1. Incidence of severe pre-eclampsia. 2. Pregnancy outcomes; GA, birthweight, Apgar score, fetal growth restriction, perinatal death. 3. Umbilical arterial blood gas.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned using a computer-generated list of random number to receive either calcium or matching placebo."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation list was maintained by pharmacy personnel; the drug and placebo were delivered by pharmacy to antepartum ward, where nurse administered the medication."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to intervention. Placebo tablets contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were blinded to treatment. Placebo tablets contained starch and were identical to calcium tablets with respect to weight, size, flavour and appearance.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During the studied period, 75 eligible subjects were identified and invited to participate; 36 (48%) were assigned to calcium and 39 (52%) to placebo. Because of decline in perinatal research support, the study was terminated three cases earlier than suggested by power analysis." Missing data = 0%.
Selective reporting (reporting bias)	Low risk	Trial was stopped before complete enrolment due to decline of research fund.
Other bias	Low risk	None identified.

Taherian 2002

Methods	Type of study: randomised controlled study. Method of treatment allocation: the sampling method was non probability convenience. Used table of random numbers to assign each case independently to 1 of 3 groups. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: Isfahan Health Centre, Iran. Time frame: April 1998 to March 2001. Eligible criteria: nulliparity, single gestation, first antenatal visit before 20 weeks of gestation, BP < 130/80 mmHg and no proteinuria by urine dipstick. Exclusion criteria: had history of cardiovascular, renal disease or endocrinologic problem, medical or obstetric complications and those with known hazardous condition (multiple gestation, hydatidiform mole). Total recruited: 990 healthy pregnant women (n = 330 participants/group).
Interventions	Group 1: received 75 mg aspirin /day, n = 330. Group 2: received 500 mg calcium carbonate/day, n = 330. Group 3: no treatment as control group, n = 330. Started treatment at 20 weeks until delivery.
Outcomes	1. BP. 2. Pregnancy outcomes; GA, birthweight, preterm birth, Apgar score, fetal growth restriction, perinatal death.
Notes	Comment: the results were reported as mean and 95% CI; we changed them into SD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The sampling method was non probability convenience. We used table of random numbers to assign each case independently to one of three groups."
Allocation concealment (selection bias)	Unclear risk	Comment: the method of allocation concealment was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Group 1 received 75 mg aspirin; group 2 received 500 mg oral calcium-D daily; and the control group 3 received no medication at all." Comment: it was impossible to blind because the difference between drug and no treatment in control group.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote:" All cases received prenatal care according to the approved model, BP, body weight and maternal height were measured." Comment: assessors were not blinded because the participants received different treatments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were included in the analyses. Missing data = 0%.

Taherian 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Villar 1987

Methods	Type of study: double-blinded, randomised controlled clinical trial. Method of treatment allocation: the women were assigned randomly in the double-blind fashion at 26 weeks' gestation to 1 of 2 treatment groups, using a randomisation schedule prepared in advance for the complete population. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: The Johns Hopkins Hospital in Baltimore and Perinatal Study Center of Rosario, Argentina. Time frame: 1983 to 1985. Eligible criteria: nulliparous, singleton, known LMP, age 18 to 30 years, free from any underlying medical disorders, negative roll-over test. Exclusion criteria: history of cardiovascular or renal disease or taking any drug. Total recruited: 52 pregnant women: *18 white: 9 in calcium group, 9 in placebo group; *34 black women: 16 in calcium group, 18 in placebo group. Total in calcium group, n = 25; in placebo group, n = 27.
Interventions	3 tablets of calcium carbonate (500 mg each). Compared with 3 placebo tablets with same size, weight, size, colour and organoleptic characteristics. Started treatment at 26 weeks.
Outcomes	1. Incidence of PIH. 2. Birthweight.
Notes	Comment: the authors provide only mean birthweight but not SD. SDs in both groups were imputed by mean.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The women were assigned randomly in the double blind fashion at 26 weeks gestation to one of two treatment groups, using a randomisation schedule prepared in advance for the complete population."
Allocation concealment (selection bias)	Low risk	Quote: "The same randomization code, standardization process, and tablets were used in both populations and code was kept in central allocation (Baltimore). Random number in closed envelopes and corresponding medication were distributing to the two hospitals at the beginning. All containers and tablets were prepared by pharmaceutical."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The women were assigned randomly in the double blind fashion at 26 weeks gestation to one of two treatment groups, using a randomisation schedule prepared in advance for the complete population."

Villar 1987 *(Continued)*

		Quote: "Placebo same size, weight, size, colour and organoleptic characteristic."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All BP value were measured by one nurse-midwife and one physician especially recruited and trained for the study." Comment: not specifically stated that outcome assessors were blinded, but placebo and treatment were identical.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were included in the analyses. Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Villar 1990

Methods	Type of study: double-blind, randomised placebo-controlled clinical trial. Method of treatment allocation: computer-generated list of random number. Opaque envelopes with the bottle number were located at the clinic and the project co-ordinator was in charge of the administration of the treatment assigned. Stratification: not stated. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 0%.
Participants	Location: Adolescent Pregnancy Clinic of the Johns Hopkins Hospital in Baltimore. Time frame: 1985 to1988. Eligible criteria: age < 17 year, GA < 20 week, singleton pregnancy, certain LMP, free from any underlying medical disorders determined by history, physical examination, and laboratory tests. Exclusion criteria: underlying medical disorders determined by history, physical examination, and laboratory tests. Total recruited: 190 adolescent pregnant women; 95 in the calcium group, 95 in the placebo group.
Interventions	2 g of calcium (4 tablets of calcium carbonate per day, 500 mg of elemental calcium) compared with 4 tablets of placebo (contained lactose and granulated starch) per day, same size, weight and colour. Started treatment at 20 weeks until delivery.
Outcomes	1. Incidence of preterm labour. 2. Incidence of low birthweight, IUGR, premature rupture of membrane, PIH. 3. Pregnancy outcomes; GA, birthweight, birth length. 4. Incidence of bacteriuria, pyelonephritis.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Villar 1990 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "A computer- generated list of random number was used to allocate the corresponding treatments."
Allocation concealment (selection bias)	Low risk	Quote: "Opaque envelope with the bottle number were locate at the clinic and project coordinator was in charge of the administration of the treatment assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment versus placebo. All participants were blinded to interventions. Placebo was the same size, weight, colour, and had the same organoleptic characteristics as the calcium tablets.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo was he same size, weight, colour, and had the same organoleptic characteristics as the calcium tablets. The investigators were blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were analysed. Missing data = 0%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Villar 2006

Methods	Type of study: multicentre, randomised, placebo-controlled, double-blind trial. Central randomisation at WHO Geneva. Method of treatment allocation: computer-generated random number blocking with randomly varying groups of 6 to 8 women and were used to restrict randomisation in the strata (country). The technique consisted of allocating consecutively numbered treatment boxes for each woman. Randomisation codes remained at the WHO Clinical trial Unit until the time of analysis and were not available to any person until the analyses were completed. Boxes and tablets were prepared and numbered by Magistra SA, GENEVA and were shipped to each centre. Stratification: yes, by country. Placebo: yes, starch tablets. Sample size calculation: not stated. Intention-to-treat analyses: yes. Losses to follow-up: 13 in 8325 = 0.16%. Before treatment started, 2 women in the calcium group were not pregnant. 2 women in the placebo group were excluded from the analyses. 143 (3.4%) in calcium group (4157-143) were lost to follow-up and no delivery information; 4008 pregnancies available for analyses. 155 (3.7%) in placebo group (4168-155) lost to follow-up and no delivery information; 4006 pregnancies available for analyses of preterm labour and 4161 pregnancies available for analyses of PIH (final analyses) of preterm labour and 4151 pregnancies available for analyses of PIH (final analyses). Post randomised exclusion: 4 in calcium were not pregnant, 5 in placebo group.
Participants	Location: Rosiario, Argentina; Assiut , Egypt; Nagpur and Vellor, India; Lima, Peru; Johannesburg, South Africa; Ho Chiminh City, Vietnam; where population intake calcium < 600 mg/d. Time frame: November 2001 to July 2003.

Villar 2006 *(Continued)*

	Eligible criteria: healthy nulliparity, normal single viable pregnancy with known menstrual period date (LMP), registering at antenatal clinic before 20 weeks of gestation. Exclusion criteria: BP > 140/90 mmHg, had history or evidence of chronic hypertension, renal disease, signs and symptoms of nephrolithiasis, parathyroid disease and disease that require digoxin, phenytoin, or tetracycline therapy. Total recruited: 8325 pregnant women were randomised, treatment group, n = 4157, control group, n = 4168.
Interventions	1.5 g of calcium carbonate (1 x 500 mg tablet, 3 times per day at meal time), chewable tablets started at 20 weeks until delivery, and > 3 hours after any iron supplement. Compared with 3 tablets of placebo (contained lactose, sorbitol, cellulose plus other calcium free ingredient) per day, same form, colour and taste.
Outcomes	1. Incidence of pre-eclampsia/eclampsia. 2. Pregnancy outcomes; GA, preterm birth, birthweight, birth length, maternal admission to intensive care unit, maternal death, stillbirth, neonatal death.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Central randomisation at WHO Geneva. Computer-generated random number blocking with randomly varying groups of 6 to 8 women and were used to restrict randomisation in the strata (country)."
Allocation concealment (selection bias)	Low risk	Quote: "The technique consisted of allocating consecutively numbered treatment boxes for each woman. Randomization codes remained at the WHO Clinical trial Unit until the time of analysis and were not available to any person until the analyses were completed. Boxes and tablets were prepared and numbered by Magistra SA, GENEVAand were shipped to each centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Women were assigned randomly to receive calcium tablets or placebo.They were identical in form, color and taste." Randomisation code kept until study end.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Women were assigned randomly to receive calcium tablets or placebo.They were identical in form, color and taste." Blood pressure was recorded by trained nurses and doctors. Randomisation code kept until study end.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 8325 women assigned randomly to group, 4157 were assigned to the calcium group and 4168 were assigned to the placebo group. Nine women (5 in the placebo group; 4 in calcium group) were determined to not be pregnant, and 2 women from each group who were lost to follow-up before starting any treatment were excluded from all analyses. Delivery information was unavailable for 143 (3.4%) in the placebo group; therefore, they did not contribute to the preterm analyses, but the available data were included in the analyses for other outcomes. Thus, 4151 women in the calcium group and 4161 women in the placebo group contribute to the final analyses." Missing data 13 in 8325 = 0.16%.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	None identified.

Wanchu 2001

Methods	Type of study: randomly assigned to 2 treatment groups. Method of treatment allocation: not stated. Stratification: not stated. Placebo: no (no treatment). Sample size calculation: not stated. Intention-to-treat analyses: no. Losses to follow-up: 20 in 120 = 16.7%.
Participants	Location: Post Graduate Institute of Medical Education and Research, Chandigarh. Time frame: not stated. Eligible criteria: uncomplicated normotensive primigravida with singleton pregnancy, GA < 20 weeks. Exclusion criteria: multiple pregnancy, molar pregnancy, hydramnios, congenital malformation, chronic hypertension, chronic renal disease, diabetes mellitus and those already on calcium supplementation. Total recruited: 120 pregnant women were enrolled, 100 who completed the protocol were analysed. 50 participants in treatment group, 50 participants in control group.
Interventions	2 g of calcium (4 tablets of calcium carbonate). Compared with no treatment. Started treatment at 20 weeks.
Outcomes	1. Incidence of PIH. 2. Pregnancy outcomes; GA, PROM, preterm birth, birthweight, IUGR, Apgar score.
Notes	No restriction was put on dietary calcium intake in either group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to ether group of two treatment groups." Comment: the method of sequence generation was not stated.
Allocation concealment (selection bias)	Unclear risk	Comment: the method of allocation concealment was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment versus no treatment. Could not blind participants.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Could not blind investigator due to different treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "120 pregnant women were enrolled in the study, 100 women who completed the protocol were analysed." Missing data = 20 in 120 = 16.7%.
Selective reporting (reporting bias)	Unclear risk	None identified.
Other bias	Low risk	None identified.

BP: blood pressure
Ca: calcium
CI: confidence interval
CS: caesarean section
g: gram
g/d: grams per day
GA: gestational age
ITT: intention-to-treat
IUGR: intrauterine growth restriction
LMP: last menstrual period
MAP: mean arterial pressure
NICU: neonatal intensive care unit
mg: milligram
mL/d: millilitres per day
mmHg: millimetres mercury
PIH: pregnancy-induced hypertension
PROM: preterm rupture of the membranes
SD: standard deviation
U/L: units per litre
WHO: World Health Organization

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

Study	Reason for exclusion
Almirante 1998	This trial was reported in abstract form only. We emailed the authors for further information at the last publication of the review (2011) and have had no reply. The study has been excluded for insufficient information.
Asemi 2012	The intervention was not relevant. The intervention was a combination of calcium and vitamin D supplementation. The study population was at risk for pre-eclampsia. The intervention took place in the third trimester. For these reasons the trial was excluded.
Chames 2002	This trial was reported in abstract form only. We emailed the authors for further information at the last publication of the review (2011) and have had no reply. The study has been excluded for insufficient information.
Diogenes 2013	The intervention was not relevant. The intervention for this trial was a combination of calcium and vitamin D.
Duggin 1974	The outcomes were not relevant and allocation to groups was not random. 7 primiparas (aged 16-19 years) who were at 32-36 weeks' gestation were included. The participants were divided into control participants (patient 1-4) and supplemented participants (patients 5-7) to measure metabolic balance.
Felix 1991	There was no random allocation to groups in this trial (women allocated to groups in sequence). The aim of the study was to examine the hypotensive effects of calcium in Andean women.
Galimberti 2001	This trial was reported in abstract form only. We emailed the authors for further information at the last publication of the review (2011) and have had no reply. The study has been excluded for insufficient information.
Hammar 1981	The participants were not appropriate. This study was aimed to determine the effect of calcium treatment in pregnant women who suffered from leg cramps; 42 pregnant women who suffered from leg cramps with gestational age 21-38 weeks were included.
Janakiraman 2003	This was a cross-over study examining bone resorption among pregnant women during received calcium supplementation. 32 pregnant women gestational age 25-35 weeks participated in the study for 20 days. Each women received 1200 mg calcium supplement for 10 days and multivitamin

Study	Reason for exclusion
	without calcium for 10 days. N-telopeptides of type I collagen (NTX), a biomarker of bone resorption were measured.
Kalkwarf 1997	The intervention was not appropriate. The study aimed to examine the effect of calcium supplementation on bone density in postpartum period. The randomised, placebo-controlled trial of 1 g calcium supplementation was conducted in 97 lactating and 99 non-lactating women a mean 16 ± 2 days postpartum (the study of lactation). The other trial (the study of weaning) 95 lactating women who weaned their infants in 2 months after enrolment and 92 non-lactating women were enrolled 5.6 ± 0.8 months postpartum.
Kent 1995	The participants were not appropriate. This was a study focusing on the postpartum period and women were not randomised to receive calcium until 36 weeks' gestation. This trial aimed to study the effect of an oral calcium supplement on regional bone loss in normal lactation women. 79 pregnant women at gestational age 36 weeks were randomised to received placebo or 500 mg twice daily of calcium through to 24 weeks' lactation.
Liu 2011	The intervention was not appropriate. The participants were provided calcium supplementation until 6 weeks postpartum and measured bone mineral density post-treatment.
Lopez-Jaramillo 1990	The participants were not appropriate.The study aimed to examine the effect of calcium supplementation on risk of PIH in pregnant women who had a positive roll-over test.
Mahomed 2000	The participants were not appropriate. The study aimed to examine the effect of calcium supplementation on risk of PIH and preterm labour in twin pregnancy.
Mazurkevich 2013	This intervention was not relevant. The intervention in this study was a combination of calcium carbonate and cholecalciferol.
Mukherjee 1997	The participants were not appropriate. The study aimed to examine the effect of calcium supplementation in reducing leg cramps in homogeneous Chinese population. All pregnant women who suffered from leg cramps during January 1994 and May 1995 were enrolled to received either calcium gluconate 600 mg twice daily or 2 multivitamin tablets twice daily.
Odendaal 1974	The participants were not appropriate. Calcium was supplemented only when participants suffered from leg cramps, which not relevant to the objective of the review.
Prentice 1995	This study did not examine calcium supplementation amongst pregnant women. 60 Gambian mothers consuming a low-calcium were randomised to receive calcium supplement or placebo from 10 days to 78 weeks postpartum.
Qui 1999	The intervention was not relevant. Calcium was supplemented from 20 weeks' gestation to postpartum 45 days.
Robinson 1947	The intervention was not appropriate. Calcium was given to treat women with leg cramps, which was not relevant to the objective of the review.

g: grams
PIH: pregnancy-induced hypertension

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

Aghamohammady 2010

Methods	Randomised controlled trial.
Participants	Healthy pregnant women age > 35. Nulliparous only, between 15-20 weeks' gestation.

Aghamohammady 2010 *(Continued)*

Interventions	2 g daily elemental calcium versus 2 g daily placebo.
Outcomes	Preterm delivery, pre-eclampsia.
Notes	This trial is reported in abstract form only with no outcome data. We have emailed the authors for additional information and outcome data.

Sulovic 2013

Methods	Randomised controlled trial.
Participants	Healthy nulliparous pregnant women between 14-23 weeks' gestation.
Interventions	Daily treatment with 2 g elemental calcium versus daily treatment with placebo.
Outcomes	Incidence of pre-eclampsia, PIH, preterm deliveries, small for gestational age births, fetal or neonatal deaths.
Notes	This trial is reported in abstract form only. We have emailed the authors for additional outcome data.

Zheng 2000

Methods	Randomised controlled trial.
Participants	Pregnant women with gestation 20-34 weeks.
Interventions	Osteoform capsules 2 tablets daily (dosage not stated) vs no treatment.
Outcomes	Serum calcium level, symptoms, PIH, IUGR.
Notes	This trial is reported in Chinese language only and has been sent for translation.

Ca: Calcium
g/d: grams per day
IUGR: intrauterine growth restriction
PIH: pregnancy-induced hypertension

DATA AND ANALYSES

Comparison 1. Calcium supplementation versus placebo or no treatment (maternal outcomes)

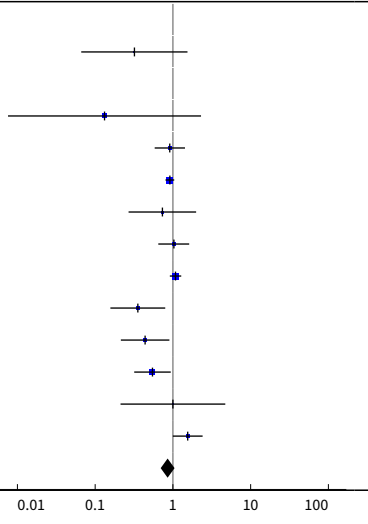
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth (a) Birth prior to 37 weeks	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Main analysis	13	16139	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
1.2 Sensitivity analysis by concealment allocation	11	15379	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
2 Preterm birth (a) Birth prior to 37 weeks by dose of calcium	13	16139	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
2.1 Low dose	1	660	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.00, 2.41]
2.2 High dose	12	15479	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 0.99]
3 Preterm birth (a) Birth prior to 37 weeks by started to take calcium	13	16073	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]
3.1 Started calcium before 20 weeks	5	13290	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.11]
3.2 Started calcium at 20 weeks or more	8	2783	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.45, 1.15]
4 Preterm birth (a) Birth prior to 37 weeks by type of calcium	13	16139	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
4.1 Carbonate	12	16047	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
4.2 Lactate	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Gluconate	1	92	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Preterm birth (b) Birth prior to 34 weeks	4	5669	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.80, 1.36]
6 Preterm birth (b) Birth prior to 34 weeks - Sensitivity analysis by concealment allocation	3	5569	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
7 Maternal weight gain (g/w)	3	404	Mean Difference (IV, Random, 95% CI)	-29.46 [-119.80, 60.89]
8 Maternal bone mineral density (g/cm^2) - First phalanx (calcium 300 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9 Maternal bone mineral density (g/cm^2) - Second metacarpal (calcium 300 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

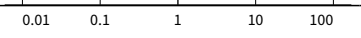
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Maternal bone mineral density (g/cm^2) - Fourth metacarpal (calcium 300 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Maternal bone mineral density (g/cm^2) - First phalanx (calcium 600 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Maternal bone mineral density (g/cm^2) - Second metacarpal (calcium 600 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Maternal bone mineral density (g/cm^2) - Fourth metacarpal (calcium 600 mg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Maternal death	2	8974	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.06, 1.38]
15 Maternal admission to intensive care unit	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
16 Vaginal birth	8	6916	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.99, 1.03]
17 Instrumental vaginal birth	2	675	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.66, 1.20]
18 Caesarean section	9	7440	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.10]

Analysis 1.1. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 1 Preterm birth (a) Birth prior to 37 weeks.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Main analysis					
Purwar 1996	2/97	6/93		1.59%	0.32[0.07,1.54]
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Boggess 1997	0/12	3/11		0.51%	0.13[0.01,2.3]
Belizan 1991	34/544	38/554		10.93%	0.91[0.58,1.43]
Villar 2006	398/4038	436/4042		20.67%	0.91[0.8,1.04]
Sanchez-Ramos 1994	5/29	8/34		3.57%	0.73[0.27,1.99]
Sanchez-Ramos 1995	18/36	19/39		10.65%	1.03[0.65,1.62]
Levine 1997	248/2295	229/2294		19.5%	1.08[0.91,1.28]
Villar 1990	7/94	20/95		5.01%	0.35[0.16,0.8]
Crowther 1999	10/227	23/229		6.02%	0.44[0.21,0.9]
Kumar 2009	19/273	32/251		8.83%	0.55[0.32,0.94]
Wanchu 2001	3/50	3/50		1.64%	1[0.21,4.72]
Taherian 2002	45/330	29/330		11.09%	1.55[1,2.41]
Subtotal (95% CI)	**8074**	**8065**		**100%**	**0.86[0.7,1.05]**

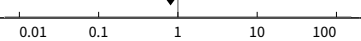


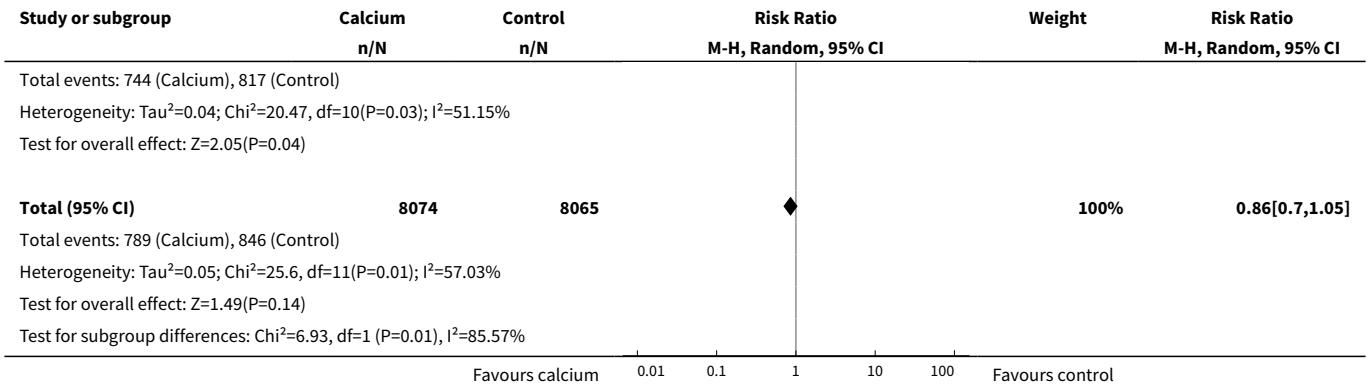
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 789 (Calcium), 846 (Control)					
Heterogeneity: Tau²=0.05; Chi²=25.6, df=11(P=0.01); I²=57.03%					
Test for overall effect: Z=1.49(P=0.14)					
1.1.2 Sensitivity analysis by concealment allocation					
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Boggess 1997	0/12	3/11		0.54%	0.13[0.01,2.3]
Belizan 1991	34/544	38/554		12.29%	0.91[0.58,1.43]
Villar 1990	7/94	20/95		5.43%	0.35[0.16,0.8]
Purwar 1996	2/97	6/93		1.69%	0.32[0.07,1.54]
Kumar 2009	19/273	32/251		9.79%	0.55[0.32,0.94]
Crowther 1999	10/227	23/229		6.57%	0.44[0.21,0.9]
Sanchez-Ramos 1994	5/29	8/34		3.84%	0.73[0.27,1.99]
Levine 1997	248/2295	229/2294		23.16%	1.08[0.91,1.28]
Villar 2006	398/4038	436/4042		24.74%	0.91[0.8,1.04]
Sanchez-Ramos 1995	18/36	19/39		11.95%	1.03[0.65,1.62]
Subtotal (95% CI)	**7694**	**7685**		**100%**	**0.8[0.65,0.99]**
Total events: 741 (Calcium), 814 (Control)					
Heterogeneity: Tau²=0.04; Chi²=20.46, df=9(P=0.02); I²=56.02%					
Test for overall effect: Z=2.08(P=0.04)					
Test for subgroup differences: Chi²=0.2, df=1 (P=0.65), I²=0%					



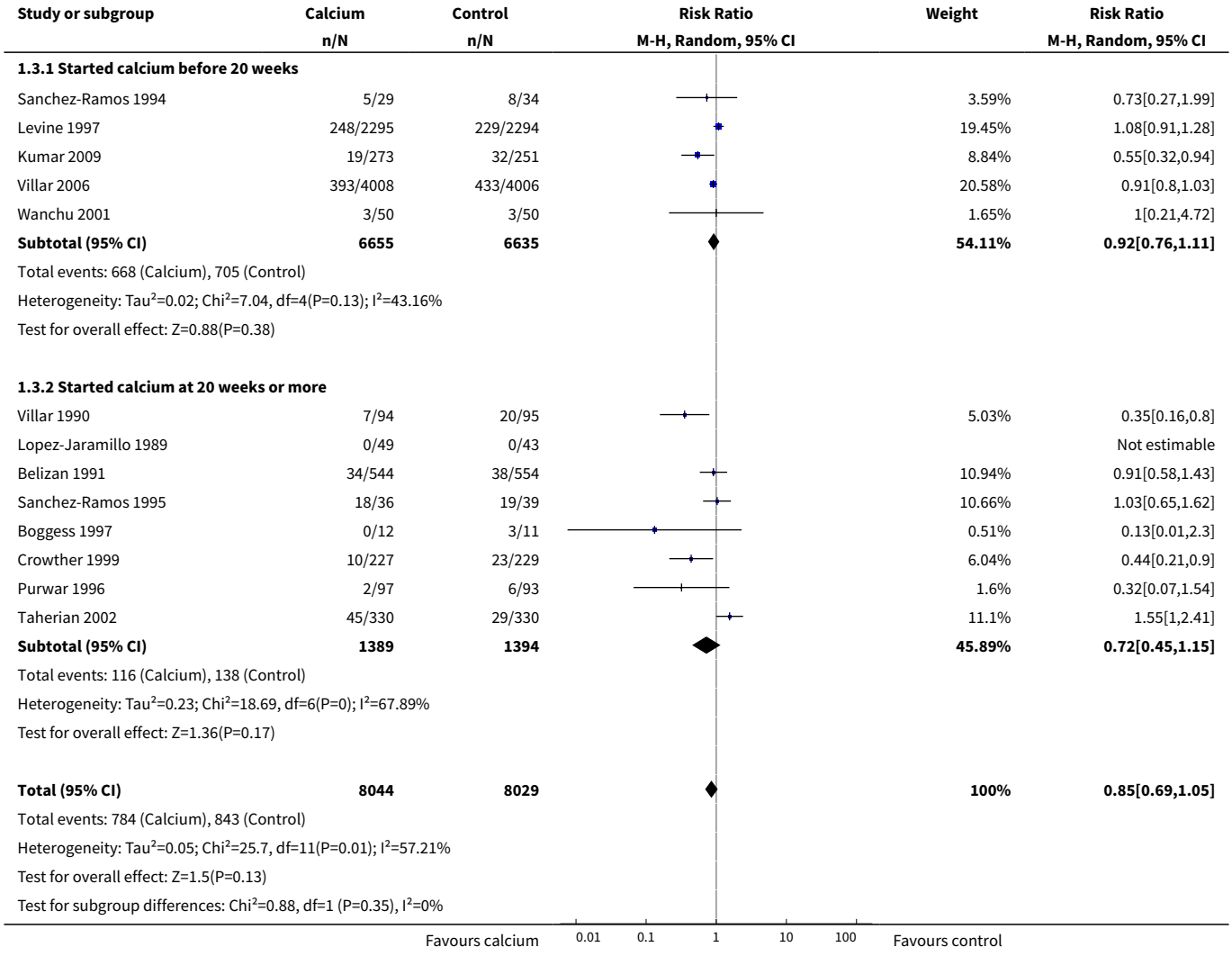
Analysis 1.2. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 2 Preterm birth (a) Birth prior to 37 weeks by dose of calcium.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Low dose					
Taherian 2002	45/330	29/330		11.09%	1.55[1,2.41]
Subtotal (95% CI)	**330**	**330**		**11.09%**	**1.55[1,2.41]**
Total events: 45 (Calcium), 29 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					
1.2.2 High dose					
Sanchez-Ramos 1994	5/29	8/34		3.57%	0.73[0.27,1.99]
Belizan 1991	34/544	38/554		10.93%	0.91[0.58,1.43]
Kumar 2009	19/273	32/251		8.83%	0.55[0.32,0.94]
Villar 2006	398/4038	436/4042		20.67%	0.91[0.8,1.04]
Boggess 1997	0/12	3/11		0.51%	0.13[0.01,2.3]
Levine 1997	248/2295	229/2294		19.5%	1.08[0.91,1.28]
Crowther 1999	10/227	23/229		6.02%	0.44[0.21,0.9]
Purwar 1996	2/97	6/93		1.59%	0.32[0.07,1.54]
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Villar 1990	7/94	20/95		5.01%	0.35[0.16,0.8]
Sanchez-Ramos 1995	18/36	19/39		10.65%	1.03[0.65,1.62]
Wanchu 2001	3/50	3/50		1.64%	1[0.21,4.72]
Subtotal (95% CI)	**7744**	**7735**		**88.91%**	**0.81[0.66,0.99]**





Analysis 1.3. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 3 Preterm birth (a) Birth prior to 37 weeks by started to take calcium.

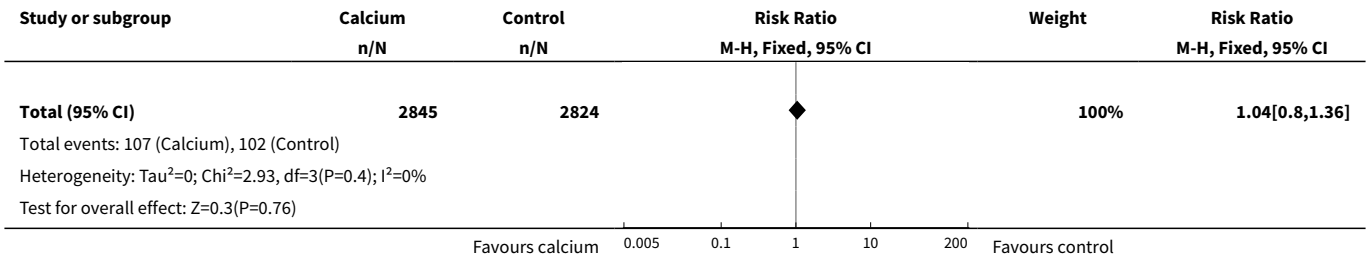


Analysis 1.4. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 4 Preterm birth (a) Birth prior to 37 weeks by type of calcium.

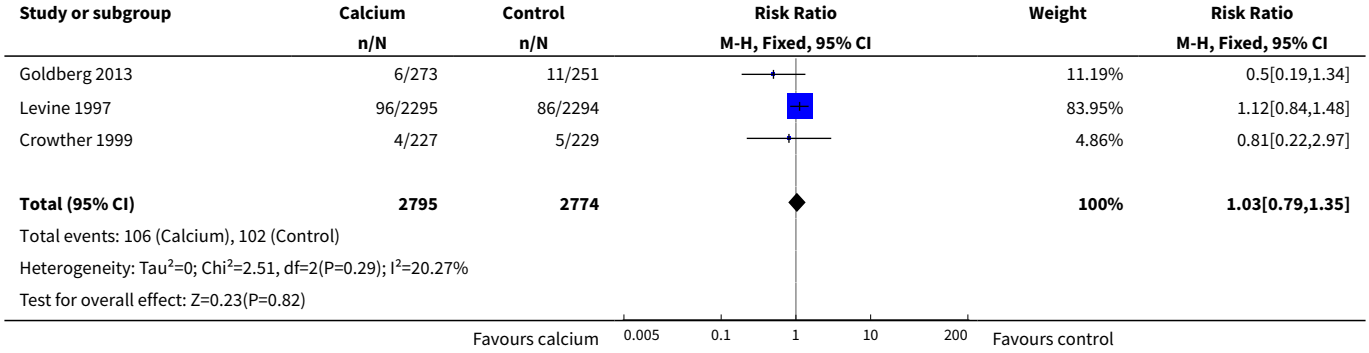
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Carbonate					
Villar 1990	7/94	20/95		5.01%	0.35[0.16,0.8]
Belizan 1991	34/544	38/554		10.93%	0.91[0.58,1.43]
Boggess 1997	0/12	3/11		0.51%	0.13[0.01,2.3]
Purwar 1996	2/97	6/93		1.59%	0.32[0.07,1.54]
Sanchez-Ramos 1994	5/29	8/34		3.57%	0.73[0.27,1.99]
Kumar 2009	19/273	32/251		8.83%	0.55[0.32,0.94]
Villar 2006	398/4038	436/4042		20.67%	0.91[0.8,1.04]
Crowther 1999	10/227	23/229		6.02%	0.44[0.21,0.9]
Sanchez-Ramos 1995	18/36	19/39		10.65%	1.03[0.65,1.62]
Levine 1997	248/2295	229/2294		19.5%	1.08[0.91,1.28]
Taherian 2002	45/330	29/330		11.09%	1.55[1,2.41]
Wanchu 2001	3/50	3/50		1.64%	1[0.21,4.72]
Subtotal (95% CI)	**8025**	**8022**		**100%**	**0.86[0.7,1.05]**
Total events: 789 (Calcium), 846 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=25.6, df=11(P=0.01); I^2=57.03%					
Test for overall effect: Z=1.49(P=0.14)					
1.4.2 Lactate					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.4.3 Gluconate					
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Subtotal (95% CI)	**49**	**43**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**8074**	**8065**		**100%**	**0.86[0.7,1.05]**
Total events: 789 (Calcium), 846 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=25.6, df=11(P=0.01); I^2=57.03%					
Test for overall effect: Z=1.49(P=0.14)					
Test for subgroup differences: Not applicable					

Analysis 1.5. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 5 Preterm birth (b) Birth prior to 34 weeks.

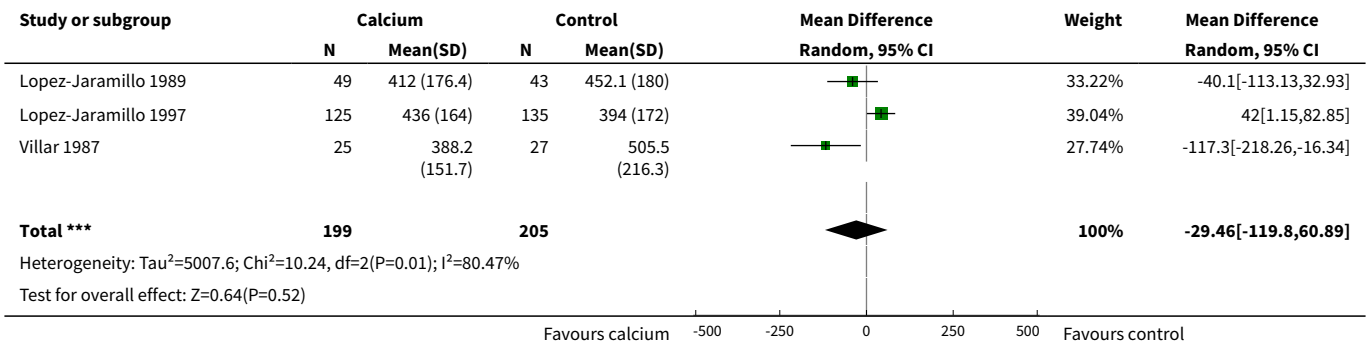
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Wanchu 2001	1/50	0/50		0.49%	3[0.13,71.92]
Crowther 1999	4/227	5/229		4.84%	0.81[0.22,2.97]
Kumar 2009	6/273	11/251		11.13%	0.5[0.19,1.34]
Levine 1997	96/2295	86/2294		83.55%	1.12[0.84,1.48]



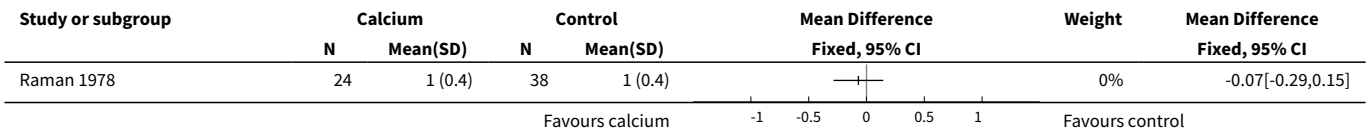
Analysis 1.6. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 6 Preterm birth (b) Birth prior to 34 weeks - Sensitivity analysis by concealment allocation.



Analysis 1.7. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 7 Maternal weight gain (g/w).



Analysis 1.8. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 8 Maternal bone mineral density (g/cm2) - First phalanx (calcium 300 mg).



Analysis 1.9. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 9 Maternal bone mineral density (g/cm²) - Second metacarpal (calcium 300 mg).

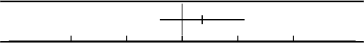
Study or subgroup	Calcium		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Raman 1978	24	1.8 (0.4)	38	1.6 (0.5)		0.19[-0.02,0.4]

Analysis 1.10. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 10 Maternal bone mineral density (g/cm²) - Fourth metacarpal (calcium 300 mg).

Study or subgroup	Calcium		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Raman 1978	24	1.3 (0.5)	38	1.3 (0.4)		0.06[-0.17,0.29]

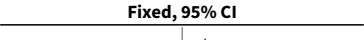
Analysis 1.11. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 11 Maternal bone mineral density (g/cm²) - First phalanx (calcium 600 mg).

Study or subgroup	Calcium		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Raman 1978	25	1.1 (0.3)	38	1 (0.4)		0.09[-0.1,0.28]



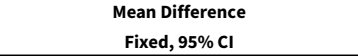
Analysis 1.12. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 12 Maternal bone mineral density (g/cm²) - Second metacarpal (calcium 600 mg).

Study or subgroup	Calcium		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Raman 1978	25	1.7 (0.5)	38	1.6 (0.5)		0.14[-0.11,0.39]



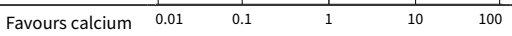
Analysis 1.13. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 13 Maternal bone mineral density (g/cm²) - Fourth metacarpal (calcium 600 mg).

Study or subgroup	Calcium		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Raman 1978	25	1.4 (0.4)	38	1.3 (0.4)		0.07[-0.13,0.27]



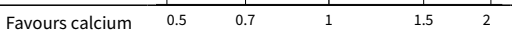
Analysis 1.14. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 14 Maternal death.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldberg 2013	1/330	1/332		14.26%	1.01[0.06,16.02]
Villar 2006	1/4151	6/4161		85.74%	0.17[0.02,1.39]
Total (95% CI)	**4481**	**4493**		**100%**	**0.29[0.06,1.38]**
Total events: 2 (Calcium), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.04, df=1(P=0.31); I^2=3.88%					
Test for overall effect: Z=1.56(P=0.12)					



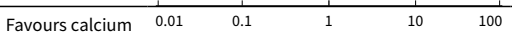
Analysis 1.15. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 15 Maternal admission to intensive care unit.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Villar 2006	116/4151	138/4161		100%	0.84[0.66,1.07]
Total (95% CI)	**4151**	**4161**		**100%**	**0.84[0.66,1.07]**
Total events: 116 (Calcium), 138 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					



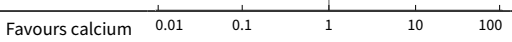
Analysis 1.16. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 16 Vaginal birth.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Belizan 1991	484/544	488/554		17.17%	1.01[0.97,1.05]
Crowther 1999	136/227	137/229		4.84%	1[0.86,1.16]
Levine 1997	1929/2295	1904/2294		67.64%	1.01[0.99,1.04]
Purwar 1996	91/97	86/93		3.12%	1.01[0.94,1.1]
Rogers 1999	84/144	44/75		2.06%	0.99[0.79,1.26]
Sanchez-Ramos 1995	25/36	27/39		0.92%	1[0.74,1.36]
Villar 1990	78/94	78/95		2.76%	1.01[0.89,1.15]
Wanchu 2001	38/50	42/50		1.49%	0.9[0.74,1.1]
Total (95% CI)	**3487**	**3429**		**100%**	**1.01[0.99,1.03]**
Total events: 2865 (Calcium), 2806 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.29, df=7(P=0.99); I^2=0%					
Test for overall effect: Z=0.87(P=0.39)					



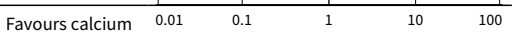
Analysis 1.17. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 17 Instrumental vaginal birth.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 1999	45/227	46/229		64.7%	0.99[0.68,1.43]
Rogers 1999	26/144	19/75		35.3%	0.71[0.42,1.2]
Total (95% CI)	**371**	**304**		**100%**	**0.89[0.66,1.2]**
Total events: 71 (Calcium), 65 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1, df=1(P=0.32); I^2=0.02%					
Test for overall effect: Z=0.76(P=0.45)					



Analysis 1.18. Comparison 1 Calcium supplementation versus placebo or no treatment (maternal outcomes), Outcome 18 Caesarean section.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Belizan 1991	60/544	66/554		11.11%	0.93[0.67,1.29]
Crowther 1999	46/227	46/229		7.78%	1.01[0.7,1.45]
Kumar 2009	41/273	27/251		4.78%	1.4[0.89,2.2]
Levine 1997	366/2295	390/2294		66.25%	0.94[0.82,1.07]
Purwar 1996	6/97	7/93		1.21%	0.82[0.29,2.35]
Rogers 1999	34/144	12/75		2.68%	1.48[0.81,2.68]
Sanchez-Ramos 1995	11/36	12/39		1.96%	0.99[0.5,1.96]
Villar 1990	16/94	17/95		2.87%	0.95[0.51,1.77]
Wanchu 2001	12/50	8/50		1.36%	1.5[0.67,3.35]
Total (95% CI)	**3760**	**3680**		**100%**	**0.99[0.89,1.1]**
Total events: 592 (Calcium), 585 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.9, df=8(P=0.66); I^2=0%					
Test for overall effect: Z=0.26(P=0.79)					



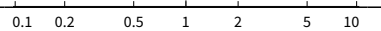
Comparison 2. Calcium supplementation versus placebo or no treatment (infant outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Low birthweight (< 2500 g)	6	14162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
2 Low birthweight (< 2500 g) by started to take calcium	6	14162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
2.1 Started calcium before 20 weeks	3	13425	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.03]
2.2 Started calcium at 20 weeks or more	3	737	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Low birthweight (< 2500 g) by type of calcium	6	14162	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
3.1 Gluconate	1	92	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Carbonate	5	14070	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.07]
4 Birthweight (g)	21	9202	Mean Difference (IV, Random, 95% CI)	56.40 [13.55, 99.25]
5 Perinatal mortality	8	15785	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
6 Stillbirth or fetal death	6	15269	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.14]
7 Admission to neonatal intensive care unit	4	14062	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
8 Birth length (cm)	7	6389	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.25, 0.06]
9 Head circumference (cm)	3	460	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.36, 0.18]
10 Intrauterine growth restriction	6	1701	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.13]
11 Neonatal bone mineral density (g/cm^2)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Total body	2	300	Mean Difference (IV, Fixed, 95% CI)	0.00 [0.00, 0.01]
11.2 Midshaft radius	1	122	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.01, 0.01]
11.3 Lumbar spine	1	256	Mean Difference (IV, Fixed, 95% CI)	0.01 [0.00, 0.02]

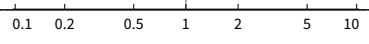
Analysis 2.1. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 1 Low birthweight (< 2500 g).

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Villar 2006	353/4151	345/4161		29.66%	1.03[0.89,1.18]
Levine 1997	188/2295	205/2294		23.99%	0.92[0.76,1.11]
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Kumar 2009	252/273	236/251		40.74%	0.98[0.94,1.03]
Villar 1990	9/94	20/95		3.37%	0.45[0.22,0.95]
Crowther 1999	6/227	17/229		2.24%	0.36[0.14,0.89]
Total (95% CI)	**7089**	**7073**		**100%**	**0.93[0.81,1.07]**
Total events: 808 (Calcium), 823 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=10.61, df=4(P=0.03); I^2=62.28%					
Test for overall effect: Z=0.99(P=0.32)					



Analysis 2.2. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 2 Low birthweight (< 2500 g) by started to take calcium.

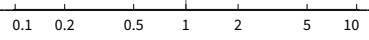
Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Started calcium before 20 weeks					
Kumar 2009	252/273	236/251		40.74%	0.98[0.94,1.03]
Villar 2006	353/4151	345/4161		29.66%	1.03[0.89,1.18]
Levine 1997	188/2295	205/2294		23.99%	0.92[0.76,1.11]
Subtotal (95% CI)	**6719**	**6706**		**94.4%**	**0.98[0.94,1.03]**
Total events: 793 (Calcium), 786 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
2.2.2 Started calcium at 20 weeks or more					
Crowther 1999	6/227	17/229		2.24%	0.36[0.14,0.89]
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Villar 1990	9/94	20/95		3.37%	0.45[0.22,0.95]
Subtotal (95% CI)	**370**	**367**		**5.6%**	**0.41[0.23,0.73]**
Total events: 15 (Calcium), 37 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=3.03(P=0)					
Total (95% CI)	**7089**	**7073**		**100%**	**0.93[0.81,1.07]**
Total events: 808 (Calcium), 823 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=10.61, df=4(P=0.03); I^2=62.28%					
Test for overall effect: Z=0.99(P=0.32)					
Test for subgroup differences: Chi^2=8.77, df=1 (P=0), I^2=88.6%					



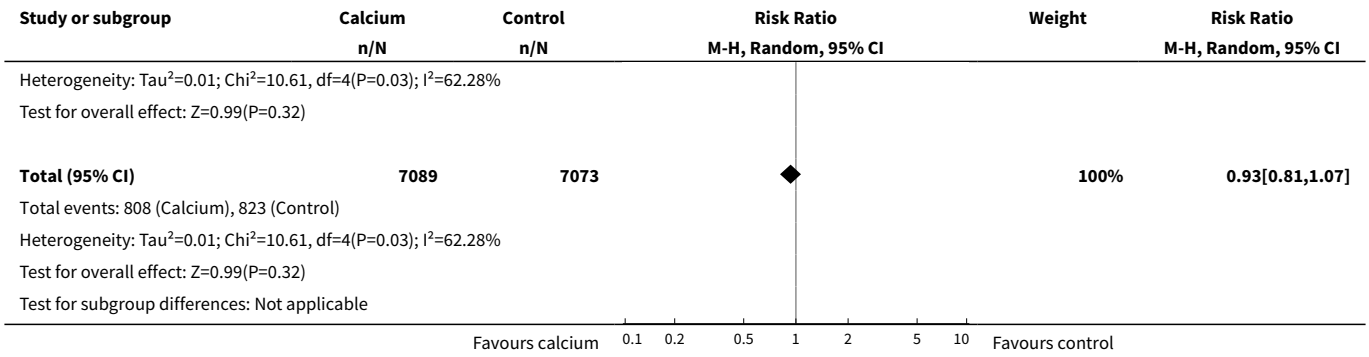
Favours calcium — Favours control

Analysis 2.3. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 3 Low birthweight (< 2500 g) by type of calcium.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Gluconate					
Lopez-Jaramillo 1989	0/49	0/43			Not estimable
Subtotal (95% CI)	**49**	**43**			**Not estimable**
Total events: 0 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.3.2 Carbonate					
Levine 1997	188/2295	205/2294		23.99%	0.92[0.76,1.11]
Villar 1990	9/94	20/95		3.37%	0.45[0.22,0.95]
Villar 2006	353/4151	345/4161		29.66%	1.03[0.89,1.18]
Kumar 2009	252/273	236/251		40.74%	0.98[0.94,1.03]
Crowther 1999	6/227	17/229		2.24%	0.36[0.14,0.89]
Subtotal (95% CI)	**7040**	**7030**		**100%**	**0.93[0.81,1.07]**
Total events: 808 (Calcium), 823 (Control)					



Favours calcium — Favours control

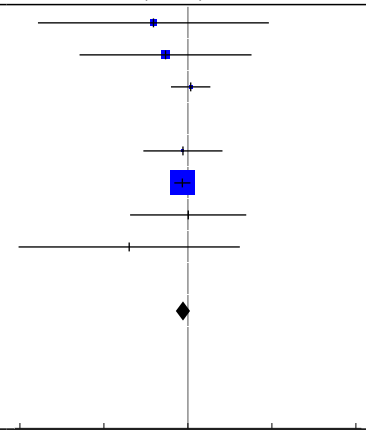


Analysis 2.4. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 4 Birthweight (g).

Study or subgroup	Calcium N	Calcium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Belizan 1983	9	2752 (409)	7	3106 (397)		1.02%	-354[-751.36,43.36]
Belizan 1983	9	3148 (154)	7	3106 (397)		1.55%	42[-268.83,352.83]
Belizan 1991	544	3200 (500)	554	3200 (400)		7.45%	0[-53.62,53.62]
Boggess 1997	11	3227 (178)	7	3145 (196)		3.41%	82[-97.3,261.3]
Chan 2006	21	3292 (165)	20	3277 (177)		5.6%	15[-89.87,119.87]
Crowther 1999	227	3323 (538)	229	3265 (570)		5.72%	58[-43.73,159.73]
Goldberg 2013	171	2900 (400)	188	2900 (400)		6.41%	0[-82.85,82.85]
Karandish 2003	33	3241 (486)	35	3011 (434)		2.63%	230[10.53,449.47]
Kumar 2009	273	2696.3 (304.1)	251	2685.4 (338)		7.4%	10.92[-44.3,66.14]
Levine 1997	2295	3192 (611)	2294	3218 (603)		7.98%	-26[-61.13,9.13]
Lopez-Jaramillo 1989	49	3097 (276)	43	2832 (318)		4.99%	265[142.5,387.5]
Lopez-Jaramillo 1997	125	2907 (183)	135	2797 (104)		7.94%	110[73.44,146.56]
Niromanesh 2001	15	3316 (308)	15	2764 (761)		0.94%	552[136.54,967.46]
Purwar 1996	97	2731 (278)	93	2626 (309)		6.38%	105[21.31,188.69]
Raman 1978	25	2600 (400)	19	2800 (310)		2.79%	-200[-409.8,9.8]
Raman 1978	24	2600 (290)	19	2800 (310)		3.36%	-200[-381.36,-18.64]
Rogers 1999	144	3190 (470)	75	3120 (560)		4.2%	70[-78.17,218.17]
Sanchez-Ramos 1994	29	3245 (414)	34	3035 (542)		2.36%	210[-26.42,446.42]
Sanchez-Ramos 1995	36	2022 (684)	39	1886 (530)		1.85%	136[-142.55,414.55]
Taherian 2002	330	3027 (417.8)	330	2909 (399.7)		7.15%	118[55.62,180.38]
Villar 1987	25	3172 (411.1)	27	3251 (444.5)		2.42%	-79[-311.54,153.54]
Villar 1990	94	3128.6 (598)	95	2939.4 (784)		3%	189.2[-9.47,387.87]
Wanchu 2001	50	2900 (400)	50	2800 (500)		3.45%	100[-77.48,277.48]
Total * **	**4636**		**4566**			**100%**	**56.4[13.55,99.25]**
Heterogeneity: Tau²=5668.7; Chi²=83.75, df=22(P<0.0001); I²=73.73%							
Test for overall effect: Z=2.58(P=0.01)							

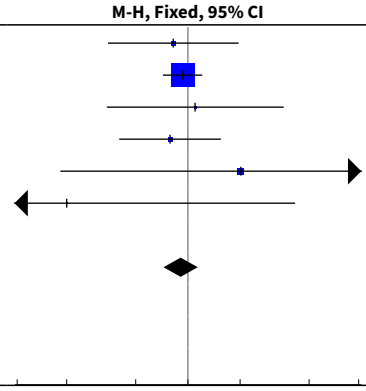
Analysis 2.5. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 5 Perinatal mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sanchez-Ramos 1994	0/29	1/34		0.67%	0.39[0.02,9.2]
Sanchez-Ramos 1995	1/36	2/39		0.93%	0.54[0.05,5.72]
Levine 1997	27/2295	25/2294		12.11%	1.08[0.63,1.85]
Lopez-Jaramillo 1997	0/125	0/135			Not estimable
Belizan 1991	6/544	7/554		3.36%	0.87[0.3,2.58]
Villar 2006	142/4181	166/4197		80.26%	0.86[0.69,1.07]
Goldberg 2013	3/330	3/332		1.45%	1.01[0.2,4.95]
Taherian 2002	0/330	2/330		1.21%	0.2[0.01,4.15]
Total (95% CI)	**7870**	**7915**		**100%**	**0.87[0.72,1.06]**
Total events: 179 (Treatment), 206 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.96, df=6(P=0.92); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					



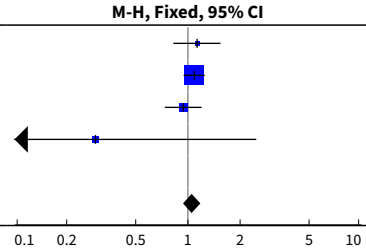
Analysis 2.6. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 6 Stillbirth or fetal death.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldberg 2013	9/330	11/332		7.24%	0.82[0.35,1.96]
Villar 2006	105/4181	113/4197		74.46%	0.93[0.72,1.21]
Kumar 2009	6/273	5/251		3.44%	1.1[0.34,3.57]
Levine 1997	15/2295	19/2294		12.55%	0.79[0.4,1.55]
Crowther 1999	2/227	1/229		0.66%	2.02[0.18,22.09]
Taherian 2002	0/330	2/330		1.65%	0.2[0.01,4.15]
Total (95% CI)	**7636**	**7633**		**100%**	**0.91[0.72,1.14]**
Total events: 137 (Calcium), 151 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.75, df=5(P=0.88); I^2=0%					
Test for overall effect: Z=0.83(P=0.41)					

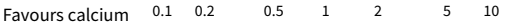


Analysis 2.7. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 7 Admission to neonatal intensive care unit.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Belizan 1991	72/544	65/554		12.58%	1.13[0.82,1.54]
Levine 1997	343/2295	315/2294		61.54%	1.09[0.94,1.25]
Villar 2006	121/4151	129/4161		25.16%	0.94[0.74,1.2]
Sanchez-Ramos 1994	1/29	4/34		0.72%	0.29[0.03,2.48]
Total (95% CI)	**7019**	**7043**		**100%**	**1.05[0.94,1.18]**

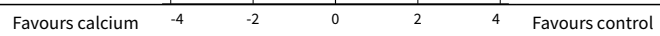


Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 537 (Calcium), 513 (Control)					
Heterogeneity: Tau²=0; Chi²=2.6, df=3(P=0.46); I²=0%					
Test for overall effect: Z=0.85(P=0.4)					



Analysis 2.8. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 8 Birth length (cm).

Study or subgroup	Calcium N	Calcium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Belizan 1991	544	49.3 (2.4)	554	49.4 (2.3)		31.15%	-0.1[-0.38,0.18]
Villar 1990	94	50.1 (3.4)	95	49.4 (4.8)		1.72%	0.7[-0.48,1.88]
Goldberg 2013	171	48.5 (2.4)	187	48.7 (2.6)		8.98%	-0.2[-0.72,0.32]
Levine 1997	2295	49.9 (3.7)	2294	50 (3.7)		52.57%	-0.1[-0.31,0.11]
Raman 1978	24	47.7 (1.9)	38	47.9 (2.2)		2.23%	-0.2[-1.24,0.84]
Karandish 2003	33	49.8 (1.8)	35	49.6 (2.5)		2.27%	0.2[-0.83,1.23]
Belizan 1983	11	48.4 (1.7)	14	48.6 (2.1)		1.09%	-0.2[-1.69,1.29]
Total * **	**3172**		**3217**			**100%**	**-0.09[-0.25,0.06]**
Heterogeneity: Tau²=0; Chi²=2.26, df=6(P=0.89); I²=0%							
Test for overall effect: Z=1.16(P=0.25)							

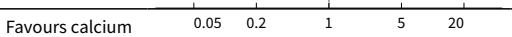


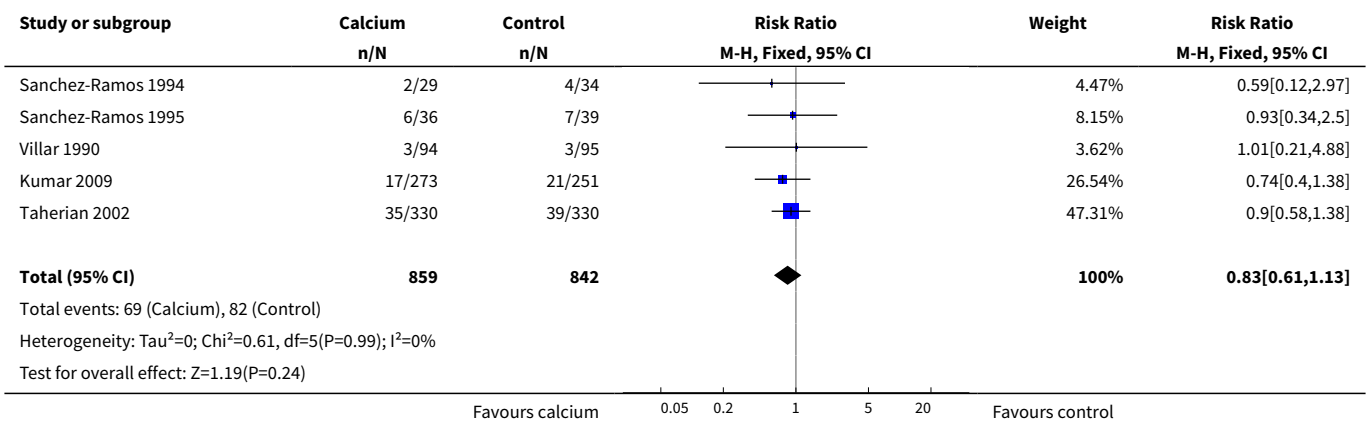
Analysis 2.9. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 9 Head circumference (cm).

Study or subgroup	Calcium N	Calcium Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goldberg 2013	172	33.9 (1.2)	188	34 (1.6)		86.02%	-0.1[-0.39,0.19]
Belizan 1983	9	33.5 (15.3)	7	33.8 (16.4)		0.03%	-0.3[-16.03,15.43]
Karandish 2003	33	34.4 (1.7)	35	34.4 (1.3)		13.92%	0[-0.72,0.72]
Belizan 1983	9	34 (16.8)	7	33.8 (16.4)		0.03%	0.2[-16.17,16.57]
Total * **	**223**		**237**			**100%**	**-0.09[-0.36,0.18]**
Heterogeneity: Tau²=0; Chi²=0.07, df=3(P=1); I²=0%							
Test for overall effect: Z=0.63(P=0.53)							

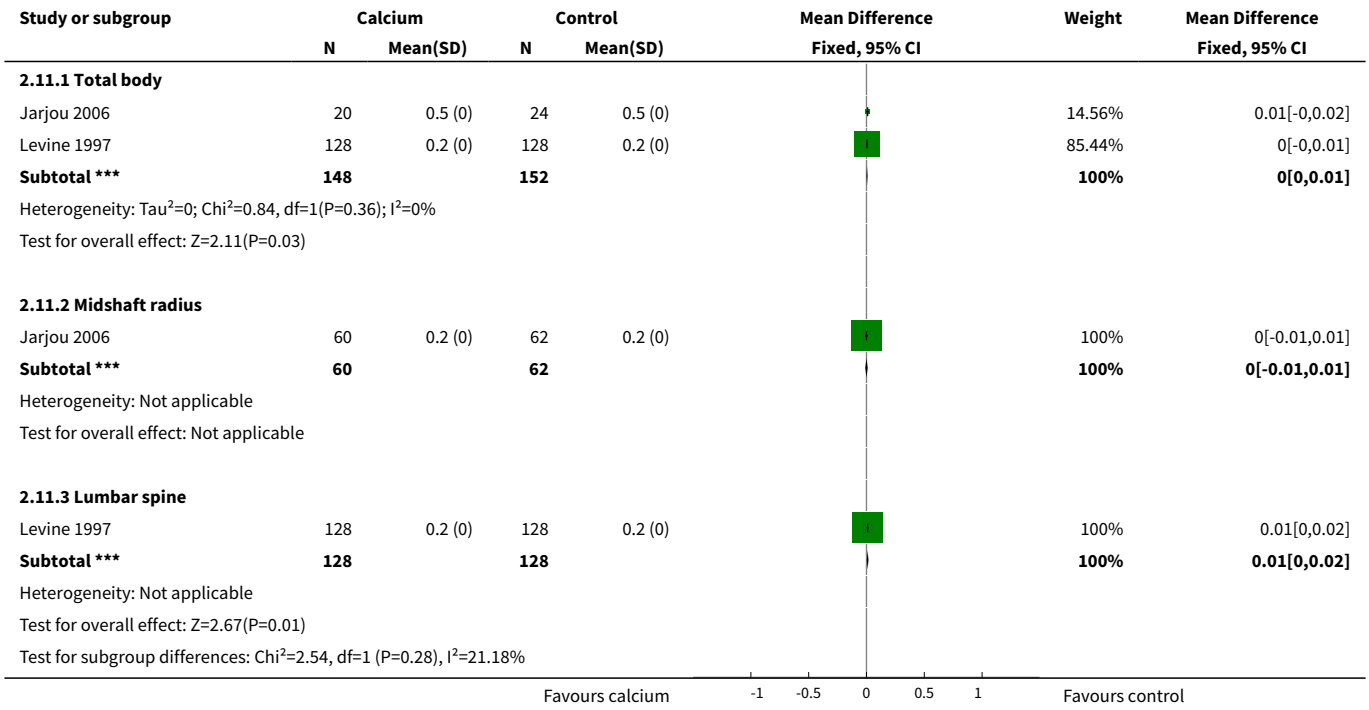
Analysis 2.10. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 10 Intrauterine growth restriction.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Purwar 1996	6/97	8/93		9.91%	0.72[0.26,1.99]





Analysis 2.11. Comparison 2 Calcium supplementation versus placebo or no treatment (infant outcomes), Outcome 11 Neonatal bone mineral density (g/cm²).



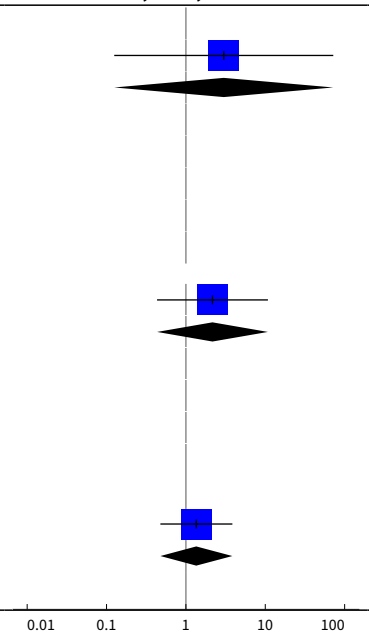
Comparison 3. Calcium supplementation versus placebo or no treatment (adverse outcomes)

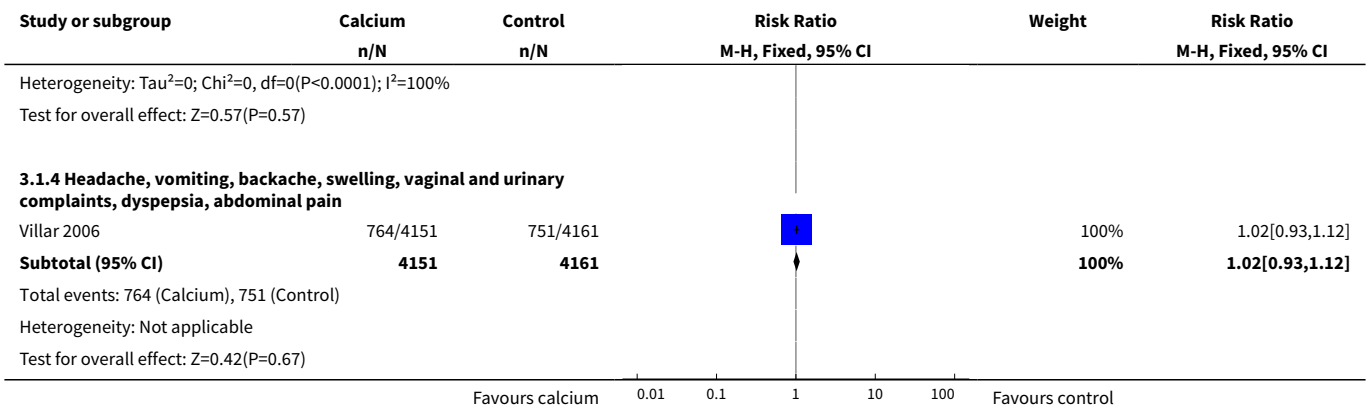
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Side effects of calcium supplementation - Maternal cholestatic jaundice	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Maternal cholestatic jaundice	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Gatrointenstinal symptoms (including nausea, heartburn and diarrhoea)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [0.43, 10.78]
1.3 Gall stones	1	518	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.48, 3.85]
1.4 Headache, vomiting, backache, swelling, vaginal and urinary complaints, dyspepsia, abdominal pain	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
2 Urinary stones	3	13419	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.48, 2.54]
3 Urinary tract infection	3	1743	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.69, 1.30]
4 Renal colic	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.40, 6.99]
5 Impaired renal function	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.51, 1.64]
6 Maternal anemia	1	1098	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.22]

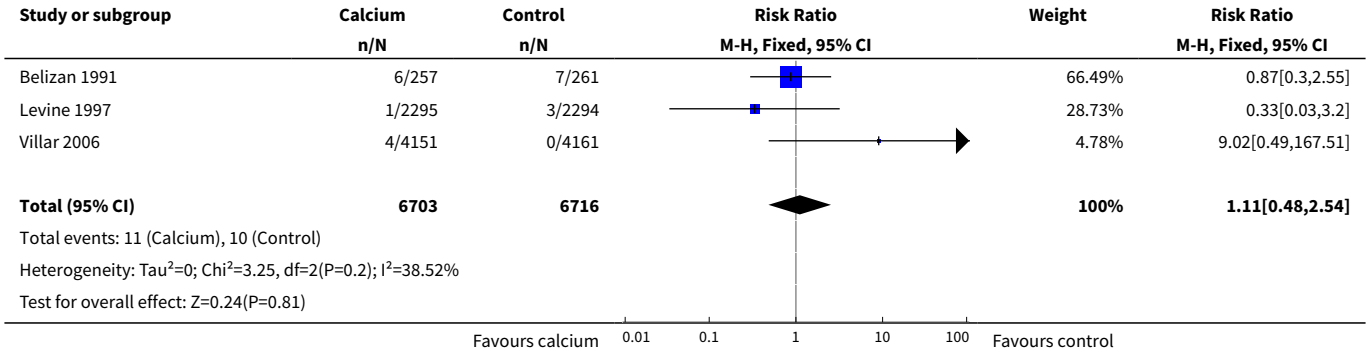
Analysis 3.1. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 1 Side effects of calcium supplementation - Maternal cholestatic jaundice.

Study or subgroup	Calcium n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Maternal cholestatic jaundice					
Wanchu 2001	1/50	0/50		100%	3[0.13,71.92]
Subtotal (95% CI)	**50**	**50**		**100%**	**3[0.13,71.92]**
Total events: 1 (Calcium), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
3.1.2 Gatrointenstinal symptoms (including nausea, heartburn and diarrhoea)					
Villar 1987	4/25	2/27		100%	2.16[0.43,10.78]
Subtotal (95% CI)	**25**	**27**		**100%**	**2.16[0.43,10.78]**
Total events: 4 (Calcium), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
3.1.3 Gall stones					
Belizan 1991	8/257	6/261		100%	1.35[0.48,3.85]
Subtotal (95% CI)	**257**	**261**		**100%**	**1.35[0.48,3.85]**
Total events: 8 (Calcium), 6 (Control)					

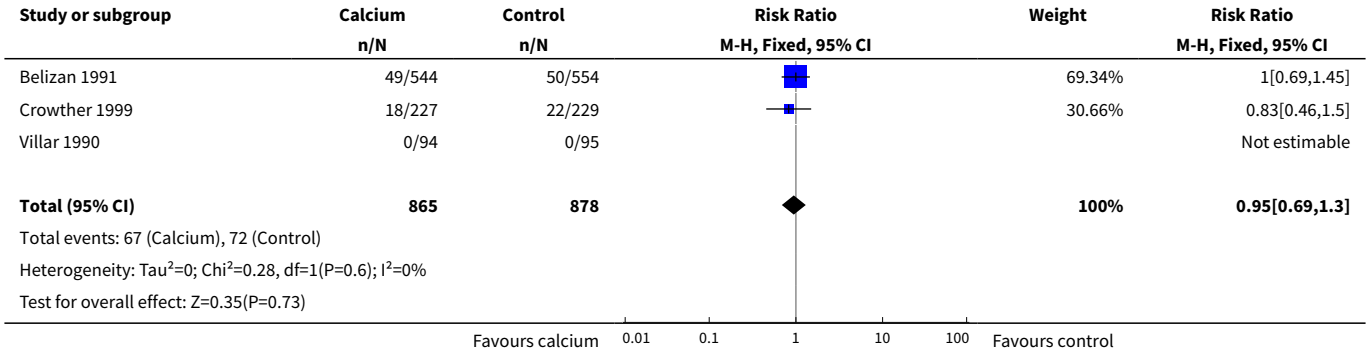




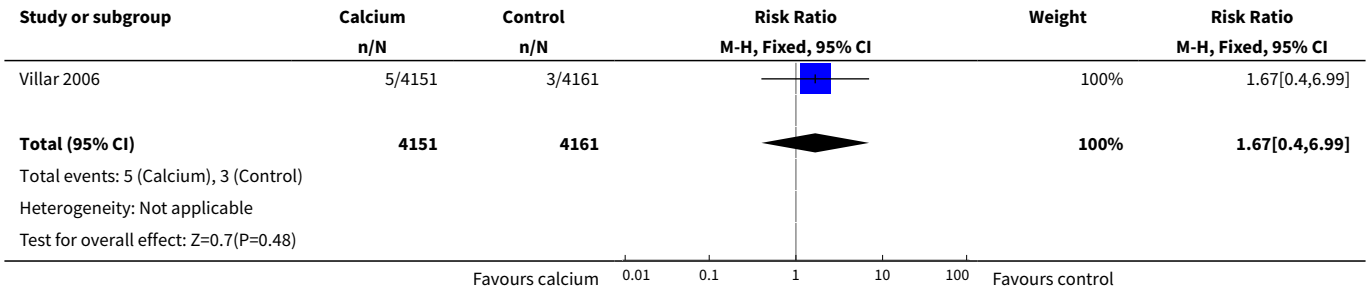
Analysis 3.2. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 2 Urinary stones.



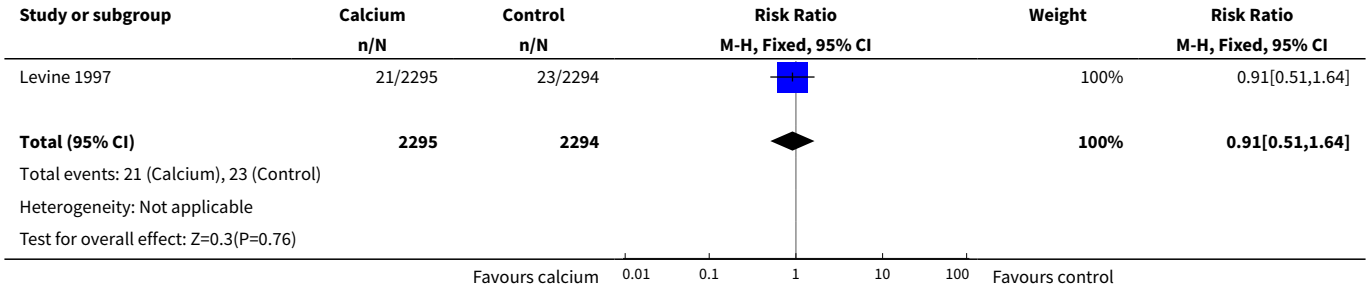
Analysis 3.3. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 3 Urinary tract infection.



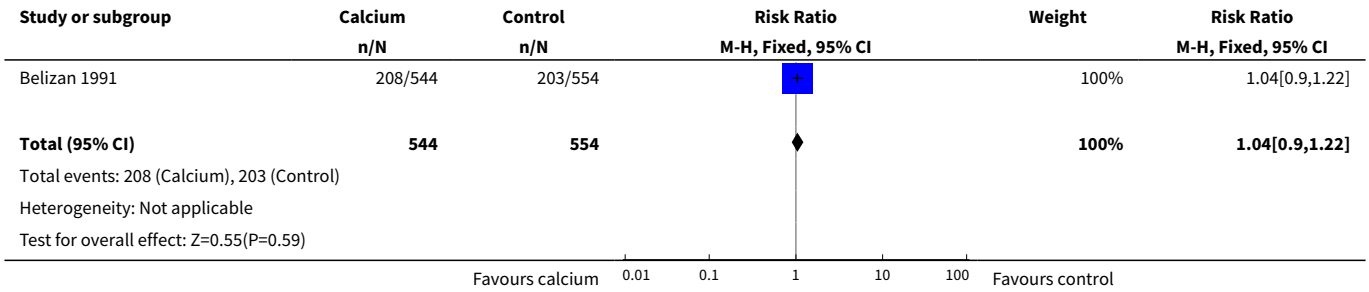
Analysis 3.4. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 4 Renal colic.



Analysis 3.5. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 5 Impaired renal function.



Analysis 3.6. Comparison 3 Calcium supplementation versus placebo or no treatment (adverse outcomes), Outcome 6 Maternal anemia.



ADDITIONAL TABLES

Table 1. Neonatal bone density (Skewed data)

Study	Outcome	Treatment			Control		
		Mean	SD	Total	Mean	SD	Total
Raman 1978 (Ca 300 mg)	Ulna	1.19	0.81	24	0.64	0.26	38
Raman 1978 (Ca 300 mg)	Fibula	1.12	0.6	24	0.65	0.41	38
Raman 1978 (Ca 300 mg)	Midshaft radius	1.17	0.62	24	0.08	0.4	38
Raman 1978 (Ca 300 mg)	Tibia	0.91	0.35	24	0.58	0.41	38
Raman 1978 (Ca 600 mg)	Ulna	1.03	0.53	25	0.64	0.26	38
Raman 1978 (Ca 600 mg)	Midshaft radius	1.17	0.65	25	0.08	0.4	38
Raman 1978 (Ca 600 mg)	Tibia	1.11	0.82	25	0.58	0.41	38
Raman 1978 (Ca 600 mg)	Fibula	1.51	0.61	25	0.65	0.41	38

The standard deviation (SD) was imputed from the standard error of a mean (SEM).

WHAT'S NEW

Date	Event	Description
30 September 2014	New citation required but conclusions have not changed	Review updated.
30 September 2014	New search has been performed	Search updated and 19 new reports were assessed for eligibility. Three new trials were included (Goldberg 2013; Herrera 2006; Kumar 2009). Four reports were abstracts added to awaiting classification, one of which requires translation (Zheng 2000). Six reports were duplicates for already included studies. Six reports were excluded. Methods updated and 'Summary of findings' table added.

CONTRIBUTIONS OF AUTHORS

P Buppasiri (PB) developed the protocol. P Lumbiganon (PL) and J Thinkhamrop (JT) edited and commented on the protocol. C Ngamjarus (CN) commented on the protocol.

For the review, PB and JT independently extracted the data. CN conducted the statistical analysis and summarised the results. PB drafted the review. All review authors commented and finalised the review.

For the updated review, PB and Nancy Medley (NM) independently extracted new data and updated the review. NM added GRADE summary. All review authors commented and finalised the update review.

DECLARATIONS OF INTEREST

Malinee Laopaiboon received an honorarium from the Thailand Research Fund which is a non-profit organisation.

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- Faculty of Public Health, Khon Kaen University, Thailand.

External sources

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- SEA-ORCHID Project, Thailand.
- Department of Nutrition for Health and Development, WHO, Switzerland.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We used stillbirth or fetal death as the same outcome, these were listed as separate outcomes in the protocol.
2. We added mode of birth (vaginal birth, instrumental birth, caesarean section), postpartum haemorrhage as secondary maternal outcomes.
3. We deleted limb pain from the list of neonatal outcomes and osteopenia and osteoporosis from the list of maternal outcomes.
4. We have modified the wording in the methods sections for Assessment of risk of bias in included studies and Assessment of reporting biases to update them with the current methods being used by the Cochrane Pregnancy and Childbirth Group. The quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating key outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; *Infant, Low Birth Weight; *Pregnancy Outcome; *Prenatal Nutritional Physiological Phenomena; Birth Weight; Calcium, Dietary [*administration & dosage] [adverse effects]; Pre-Eclampsia [prevention & control]; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Sensitivity and Specificity

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy