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

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[Intervention Review]

Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

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ABSTRACT

Background

Pre-eclampsia and eclampsia are common causes of serious morbidity and death. Calcium supplementation may reduce the risk of pre-eclampsia through a number of mechanisms, and may help to prevent preterm labour.

Objectives

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

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group Trials Register (February 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library,* 2005, Issue 4), and contacted study authors.

Selection criteria

Randomised trials comparing at least one gram daily of calcium during pregnancy with placebo.

Data collection and analysis

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

Main results

Twelve studies of good quality were included. The risk of high blood pressure was reduced with calcium supplementation rather than placebo (11 trials, 14,946 women: relative risk (RR) 0.70, 95% confidence interval (CI) 0.57 to 0.86). There was also a reduction in the risk of pre-eclampsia associated with calcium supplementation (12 trials, 15,206 women: RR 0.48, 95% CI 0.33 to 0.69). The

effect was greatest for high-risk women (5 trials, 587 women: RR 0.22, 95% CI 0.12 to 0.42), and those with low baseline calcium intake (7 trials, 10,154 women: RR 0.36, 95% CI 0.18 to 0.70).

The composite outcome maternal death or serious morbidity was reduced (4 trials, 9732 women; RR 0.80, 0.65 to 0.97). Almost all the women in these trials were low risk and had a low calcium diet. Maternal deaths were reported in only one trial. One death occurred in the calcium group and six in the placebo group, a difference which was not statistically significant (RR 0.17, 95% CI 0.02 to 1.39).

There was no overall effect on the risk of preterm birth (10 trials, 14,751 women: RR 0.81, 95% CI 0.64 to 1.03), or stillbirth or death before discharge from hospital (10 trials 15,141 babies; RR 0.89, 95% CI 0.73 to 1.09).

Blood pressure in childhood has been assessed in one study: childhood systolic blood pressure greater than 95th percentile was reduced (514 children: RR 0.59, 95% CI 0.39 to 0.91).

Authors' conclusions

Calcium supplementation appears to almost halve the risk of pre-eclampsia, and to reduce the rare occurrence of the composite outcome 'death or serious morbidity'. There were no other clear benefits, or harms.

PLAIN LANGUAGE SUMMARY

Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

Calcium supplements help prevent pre-eclampsia, lowers the risk of the woman dying or having serious problems.

Pre-eclampsia is a major cause of death in pregnant women and newborn babies worldwide. Preterm birth (birth before 37 weeks) is often caused by high blood pressure and is the leading cause of newborn deaths, particularly in low-income countries. The review of trials found that calcium supplementation during pregnancy is a safe and relatively cheap means of reducing the risk of pre-eclampsia in women at increased risk, and women from communities with low dietary calcium. Women were also less likely to die or have serious problems due to pre-eclampsia. No adverse effects have been found but further research is needed into the ideal dosage for supplementation.

BACKGROUND

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

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

During early pregnancy, blood pressure normally falls, climbing slowly in later pregnancy to reach pre-pregnancy levels at term (Villar 1989). These normal changes in blood pressure make the diagnosis of hypertension during pregnancy difficult. Clinical methods of measuring blood pressure are also subject to considerable inaccuracy (Villar 2004). A widely accepted definition, however, is a diastolic blood pressure equal to or greater than 90 mmHg before the onset of labour, or an increase in systolic blood pressure of 30 mmHg or more, or in diastolic blood pressure of 15 mmHg or more. The consequences of high blood pressure are more serious if there is associated proteinuria. Hypertension and significant proteinuria (2+ by dipstick testing, equal to or greater than 300 mg per 24 hours, or equal to or greater than 500 mg per litre) usually indicate the presence of pre-eclampsia. Recently, the urine protein to creatinine ratio has been used increasingly as a measure of proteinuria (Yamasmit 2004). Predictors of poor outcome include low gestational age and high levels of proteinuria (von Dadelszen 2004).

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980 (Belizan

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

Low calcium intake may cause high blood pressure by stimulating either parathyroid hormone or renin release, thereby increasing intracellular calcium in vascular smooth muscle (Belizan 1988) and leading to vasoconstriction. A possible mode of action for calcium supplementation is that it reduces parathyroid release and intracellular calcium, and so reduces smooth muscle contractility. By a similar mechanism, calcium supplementation could also reduce uterine smooth muscle contractility and prevent preterm labour and delivery (Villar 1990). Calcium might also have an indirect effect on smooth muscle function by increasing magnesium levels (Repke 1989).

Calcium supplementation is attractive as a potential intervention to reduce the risk of a woman developing pre-eclampsia. Furthermore, the possibility of a protective effect on the risk of hypertension during childhood makes this even more important (Belizan 1997). It is relatively cheap and readily available. Also, it is likely to be safe for the woman and her child, although this safety would need to be clearly demonstrated in pregnant women before any attempt at widespread introduction into clinical practice. A theoretical risk of increased renal tract stone formation has not been substantiated, and no other adverse effects of calcium supplementation have been documented.

This hypothesis was tested in several randomised trials commencing in the late 1980s which suggested a promising beneficial effect for calcium supplementation. The first systematic reviews highlighted the need for larger trials to assess the effects on important clinical outcomes in addition to pre-eclampsia and preterm delivery, such as perinatal mortality (Carroli 1994; Duley 1995). A subsequent systematic review (Bucher 1996) came to more enthusiastic conclusions, but this optimism was not confirmed by a large trial in the USA (CPEP 1997). These discrepancies have elicited discussion in the literature (Villar 2000). More recently, a large trial in communities with low dietary calcium intake has been reported (WHO 2006).

There is thus a need for an updated systematic review of the current evidence concerning the effectiveness of calcium supplementation in pregnancy.

OBJECTIVES

To determine, from the best available evidence, the effect of calcium supplementation during pregnancy on the risk of high blood pressure and related maternal and fetal or neonatal adverse outcomes. Subgroup analyses tested whether these effects were influenced by whether:

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

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing trials with random allocation to calcium supplementation during pregnancy versus placebo (*see* 'Methods of the review'). Quasi-random designs were excluded.

Types of participants

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

Prespecified subgroups to be compared.

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

Types of interventions

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

We limited the initial analysis to intended supplementation with at least one gram of calcium per day. Future updates of this review will include an analysis of effect by dosage, including lower dosage regimens.

Types of outcome measures

In the original protocol we prespecified 15 clinical measures of maternal and fetal or neonatal morbidity and mortality. In October 2004 we added seven additional outcomes (marked * below):

For the women

(1) High blood pressure as defined by trial authors, with or without proteinuria. Ideally, high blood pressure would be defined as diastolic blood pressure equal to or greater than 90 mmHg, or an increase in systolic blood pressure of 30 mmHg or more, or in diastolic blood pressure of 15 mmHg or more.

(2) High blood pressure with significant proteinuria, as defined by trial authors. Ideally, proteinuria would be defined as 2+ by dipstick testing, equal to or greater than 300 mg per 24 hours, or equal to or greater than 500 mg per litre. Although the strict definition of pre-eclampsia includes confirmation of no hypertension or proteinuria outside pregnancy, for convenience the above definition will be referred to in this review as pre-eclampsia.

(3) Maternal death or serious morbidity. Serious morbidity includes eclampsia; renal failure; syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome); and admission to intensive care. This will be a composite outcome of death or at least one measure of serious morbidity. In addition each individual outcome will be presented.

(4) Placental abruption.

(5) Caesarean section.

(6) *Proteinuria.

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

(8) *Eclampsia.

(9) *HELLP syndrome.

(10) *Intensive care unit admission.

(11) *Maternal death.

(12) Mother's hospital stay seven days or more.

For the child

(13) Preterm birth (birth before 37 weeks of estimated gestation).

(14) Low birthweight (the first weight obtained after birth less than 2500 g).

(15) Neonate small-for-gestational age as defined by trial authors.

(16) Admission to neonatal intensive care unit (ICU).

(17) Neonate in intensive care unit seven days or more.

(18) Stillbirth or death before discharge from hospital.

(19) *Death or severe neonatal morbidity.

Long-term outcomes

(20) Childhood disability.

(21) Systolic blood pressure greater than 95th percentile during childhood.

(22) Diastolic blood pressure greater than 95th percentile during childhood.

The primary outcomes are high blood pressure, pre-eclampsia, preterm birth, admission to neonatal intensive care unit, and stillbirth of neonatal death. Subgroup analyses are limited to the primary outcomes.

Only those outcomes with data appear in the analysis table.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (February 2006).

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

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

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

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library,* 2005, Issue 4) using the terms calcium AND pregnan* AND (hypertens* or blood press*).

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

We did not apply any language restrictions.

Data collection and analysis

Two review authors independently assessed the methodological quality and other inclusion criteria of the identified trials. At least one of these authors had no involvement in the trial. We resolved disagreements by consensus. The primary assessment for inclusion was based on concealment of allocation and whether the trial was placebo controlled.

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

We compared categorical data using relative risks and their 95% confidence intervals. We tested for statistical heterogeneity between trials using the I-squared statistic, with values greater than 50% indicating significant heterogeneity. In the absence of significant heterogeneity, data were pooled using a fixed-effect model. If there was significant heterogeneity, a random-effects model was used and an attempt made to identify potential sources of heterogeneity (Greenland 1994; Villar 1995) based on subgroup analyses by risk of hypertensive disorders, baseline dietary calcium intake, trial quality and trial size.

For continuous data, we calculated pooled estimates of effect size from a weighted average, with weight based on the inverse of the variance (Early Breast Ca 1990). We identified comparisons, outcomes and subgroups other than those prespecified in the original protocol as 'post hoc' analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We included twelve studies. Four were multicentre studies, one in Argentina (Belizan 1991), one in the USA (CPEP 1997), another in Australia (Crowther 1999) and the fourth was international (WHO 2006). Most of the 15,206 women recruited to these studies were low risk (14,619 women) and had a low dietary intake of calcium (10,154). Most studies only recruited women who were nulliparous or primiparous. One study did not state the parity of women recruited (Niromanesh 2001) and another commented that most women were nulliparous (Villar 1990). For most studies the intervention was 1.5 g to 2 g per day of calcium.

One included study has conducted long-term follow up of the children whose mothers were recruited to these trials (Belizan 1991). In this study, only the subset of women recruited in private clinics were contacted.

One other study has reported outcome for a small subset of women (CPEP 1997), but these data did not meet the inclusion criteria for this review.

Twenty-three studies were excluded from the review.

Risk of bias in included studies

See table of 'Characteristics of included studies'. All were well designed, double-blind, placebo-controlled trials. Prespecified outcome data were not available from all trials. The possibility of reporting bias must be kept in mind for those outcomes with unreported data from some trials.

In Lopez-Jaramillo (L-Jaramillo 1990), a large discrepancy in numbers allocated to each group is not accounted for.

In some trials, individual denominators were not given for specific outcomes. Where it was clear that the outcomes were not measured in the entire group, we have adjusted the denominators accordingly.

In other respects, the methodology of the studies included appears sound.

Effects of interventions

We included twelve studies. Significant heterogeneity of results occurred for four outcomes: pre-eclampsia; high blood pressure; preterm birth and birthweight less than 2500 g. Factors accounting for the heterogeneity appeared to be maternal risk at trial entry and dietary calcium. The small trials have more extreme results than large trials, but as all the small trials recruited high-risk women this could also be related to risk status. In view of the heterogeneity, we used a random-effects model for these four outcomes.

(1) High blood pressure with or without proteinuria

The results follow a similar pattern to those for pre-eclampsia (*see* below). Overall there was less high blood pressure with calcium supplementation rather than placebo (11 trials, 14,946 women: relative risk (RR) random-effects model 0.70, 95% confidence interval (CI) 0.57 to 0.86). The reduction in relative risk was greatest for the small trials (fewer than 400 women: 7 trials, 675 women, RR 0.38, 95% CI 0.21 to 0.68), for women at high risk of developing pre-eclampsia (4 trials, 327 women: RR 0.47, 95% CI 0.22 to 0.97), and for those with low baseline dietary calcium (6 trials, 9894 women: RR 0.47, 95% CI 0.29 to 0.76).

(2) Pre-eclampsia

Overall, there was a reduction in the risk of pre-eclampsia (12 trials, 15,206 women: RR 0.48, 95% CI 0.33 to 0.69). This reduction in relative risk was greatest for women at high risk of pre-eclampsia (5 trials, 587 women: RR 0.22, 95% CI 0.12 to 0.42), and for

those with low baseline calcium intake (7 trials, 10,154 women: RR 0.36, 95% CI 0.18 to 0.70).
When subgrouped by both dietary calcium intake and study size, the effect size appeared to be associated most strongly with study size (in the small studies, relative risks 0.21 for the low calcium trials and 0.26 for the adequate calcium trials, and in the large studies 0.87 and 0.70 respectively).

(3) Maternal death or serious morbidity

The relative risk of having the composite outcome maternal death or serious morbidity was reduced for women allocated calcium supplementation compared with placebo (4 trials, 9732 women: RR 0.80, 95% CI 0.65 to 0.97).

(4) Placental abruption

In the five trials reporting this outcome, there was no clear difference between the groups (14,309 women: RR 0.86 95% CI 0.55 to 1.34).

(5) Caesarean section

There was no statistically significant effect on the relative risk of caesarean section (7 trials, 14,710 women: RR 0.95, 95% CI 0.88 to 1.01).

6) *Proteinuria

Proteinuria was reported in only one trial (WHO 2006), and there was no overall difference between the groups (8312 women: RR 1.04, 95% CI 0.86 to 1.26).

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

Severe pre-eclampsia was reported in only one trial (WHO 2006). Again, there was no clear difference between the groups (1 trial, 8302 women: RR 0.74, 95% CI 0.48 to 1.15).

(8) *Eclampsia

Eclampsia was reported by the two largest trials (CPEP 1997; WHO 2006). There was no clear difference between the groups (2 trials, 12,901 women: RR 0.73, 95% CI 0.41 to 1.27).

(9) *HELLP syndrome

HELLP syndrome was also reported only by the two largest studies (CPEP 1997; WHO 2006). The relative risk was higher for women allocated calcium supplementation, rather than placebo (2 trials, 12,901 women: RR 2.67, 95% CI 1.05 to 6.82).

(10) *Maternal intensive care unit admission

Admission to intensive care was reported only by one trial (WHO 2006). There was no clear difference between the groups (1 trial, 8312 women: RR 0.84, 95% CI 0.66 to 1.07).

(11) *Maternal death

Maternal deaths were reported only by one trial (WHO 2006). One death occurred in the calcium group and six in the placebo group, a difference which was not statistically significant (RR 0.17, 95% CI 0.02 to 1.39).

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

Data were not available for this outcome.

(13) Preterm birth

There was no overall effect on preterm birth (10 trials 14,751 women; RR 0.81, 95% CI 0.64 to 1.03). However, the relative risk of preterm birth was reduced amongst women at high risk of developing pre-eclampsia recruited to four small trials (568 women: RR 0.45, 95% CI 0.24 to 0.83).

(14) Birthweight less than 2500 g

There was no overall effect on the risk of having a baby with birthweight less than 2500 g (8 trials, 14,359 women: RR 0.84, 95% CI 0.68 to 1.03).

(15) Neonate small-for-gestational age

There was no overall effect on the relative risk of the baby being born small-for-gestational age (3 trials 13,091 women: RR 1.10, 95% CI 0.88 to 1.37).

(16) Admission to neonatal intensive care unit

There was no overall effect on the relative risk of admission to a neonatal intensive care unit (4 trials 13,406 women: RR 1.05, 95% CI 0.94 to 1.18).

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

Data were not available for this outcome.

(18) Stillbirth or death before discharge from hospital

There was no overall effect on the relative risk of a stillbirth or the baby dying before discharge from hospital (10 trials, 15,141 women: RR 0.89 95% CI 0.73 to 1.09).

(19) *Death or severe neonatal morbidity

No data were available for this outcome.

(20) Childhood disability

Data were not available for this outcome.

(21) Childhood systolic blood pressure greater than 95th percentile

One trial has assessed during childhood a subset of the children recruited whilst in utero (Belizan 1991). At about seven years of age diastolic blood pressure greater than 95th percentile was reduced (1 trial, 514 women: RR 0.59, 95% CI 0.39 to 0.91). While the baseline calcium intake in the original study was low (calcium group mean 646 mg, standard deviation (SD) 396, placebo group 642, SD 448 in a sample assessed during the first four months of the study), the group followed up were only from among the 614 women from the private hospital, not the 580 from the public hospitals. Their dietary calcium intake may have differed from the mean (more likely to be higher in more affluent women). The baseline calcium status of the women in this part of the study therefore cannot be classified.

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

(22) Childhood diastolic blood pressure greater than 95th percentile

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

DISCUSSION

Calcium supplementation with at least one gram of calcium is associated with a halving in the relative risk of pre-eclampsia, with the confidence intervals putting the true effect anywhere between a 31% reduction and a 67% reduction. Women with an adequate dietary intake of calcium were the only subgroup for which this was not statistically significant, nevertheless the point estimate for this subgroup of women was a 38% reduction. The greatest reduction in risk was for women at high risk and those with low baseline dietary calcium intake. There was also a 30% reduction in the risk of gestational hypertension, with again the greatest effect being amongst women at high risk and those with a low calcium intake at trial entry. There was no overall effect on the relative risk of preterm birth, although a moderate reduction associated with calcium supplementation remains possible. There was a halving in the relative risk of preterm birth for women at high risk of pre-eclampsia. This result should be interpreted with caution, as the numbers of women in the subgroup are small and the result may therefore reflect the play of chance.

Although pre-eclampsia was reduced, this was not clearly reflected in any reduction in severe pre-eclampsia, eclampsia, or admission to intensive care. Nevertheless, the point estimates for these outcomes favoured calcium supplementation, and so moderate reductions in these outcomes remain possible. Also, the relative risk of the composite outcome 'maternal death or severe morbidity' was reduced by 20% (95% CI 35% to 3%) for women allocated calcium supplementation. In the two trials reporting HELLP syndrome, the relative risk of this outcome seemed to be increased in association with calcium supplementation.

No side-effects of calcium supplementation have been recorded in the trials reviewed. There is little information about the long-term follow up of children within these trials, with the exception of a reduction in childhood systolic hypertension in the one study to measure this outcome. There is no information about any possible changes in the use of healthcare resources associated with calcium supplementation. It would seem plausible that a reduction in gestational hypertension and pre-eclampsia might lead to fewer antenatal visits, less admission for antenatal care and fewer inductions of labour. However, these trials do not provide data on these outcomes.

Heterogeneity in the results seems to be largely associated with study size, with the small studies having the most positive results. As the small studies tended to recruit high risk women, at least some of the heterogeneity may be explained by calcium having a greater, effect for high-risk women. An alternative explanation may be that there is publication bias, with small studies that failed to report an effect for calcium supplementation not being published. The data on heterogeneity related to sample size should be interpreted with caution, as the sensitivity analysis was post-hoc, and the cut-off point for sample size (400) was arbitrary.

There are no clear differences in any other outcomes, although for several outcomes the confidence intervals are approaching statistical significance. So, for caesarean section, a small (5%) reduction in relative risk associated with calcium supplementation is possible. For preterm birth, the point estimate is for a 19% reduction in risk, and for stillbirth and death before discharge from hospital 11%, although for both these outcomes no effect or a small increase in risk has not been excluded.

Taken together, these trials show a halving in the relative risk of pre-eclampsia. This is reflected in more modest reductions in the relative risk of gestational hypertension and of maternal death or serious morbidity. There are no clear effects on other substantive outcomes at discharge from hospital

These modest results contrast with the large epidemiological differences between populations with adequate and low dietary calcium intake (Belizan 1980; Hamlin 1952; Hamlin 1962). Possible explanations include the following:

(1) Dietary calcium may be a marker for other aetiological factors.

(2) Starting supplementation in the middle trimester of pregnancy may be too late to be fully effective.

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

AUTHORS' CONCLUSIONS

Implications for practice

The reduction in pre-eclampsia, and in maternal death or severe morbidity, support the use of calcium supplementation, particularly for those with low dietary intake.

Implications for research

Any future trials should collect information about the use of health service resources, as well as other clinical outcomes. The minimum dose in this review was one gram of calcium daily. It would now be relevant to assess whether supplementation via dietary modification, for women with low calcium intake, has the same benefits as the tablets administered in these trials.

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

Research into the effects of calcium supplementation combined with low-dose aspirin would be of interest.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Belizan 1991

Methods	Multicentre trial. Numbered, sealed opaque envelopes, containing randomisation codes. Of 593 (calcium) vs 601 (placebo) enrolled, 14 vs 13 were lost before starting treatment and excluded from analysis; 577 vs 588 had at least partial follow up. Follow up was incomplete for 52 vs 46, but delivery data were available in 17 vs 12 of these, giving delivery data for 544 vs 554.
Participants	Nulliparous women, < 20 weeks pregnant; blood pressure < 140/90 mmHg (mean of 5 measurements); no present or past disease; not taking medication; normal oral glucose tolerance tests.
Interventions	2 g calcium as 500 mg calcium carbonate tablets, vs identical looking placebo tablets. Compliance was 84% (calcium) and 86% (placebo).
Outcomes	Gestational hypertension (DBP 90 or more; SBP 140 or more mmHg, on 2 occasions 6 hours apart); pre-eclampsia (gestational hypertension + proteinuria > 0.3 g/L on 2 random urine samples 6 hours apart); BP measured with random-zero sphygmomanometers, Korotkoff sound 5. Perinatal death. Follow up: BP > 95th percentile for sex, age and height for children 5-9 years.
Notes	Three hospitals in Rosario, Argentina. Data for preterm birth given as percentages, not clear what the denominators were. Assumed to be the numbers with complete follow up (527 vs 542) as these were the numbers which were divisible by the percentages to give whole numbers. Babies born in the private hospitals followed up at 7 years. Of 614 randomised (calcium 309/placebo 305), 301/299 completed the first study, 2/6 infant deaths and 1/0 maternal deaths had occurred, leaving 298/293 eligible for follow up. 289/285 were contacted, 10/5 refused to participate, 22/19 lived outside the country, and 257/261 were assessed (88% of those eligible).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

CPEP 1997

Methods	Numbered treatment packs in computer-generated simple randomisation sequence. Loss to follow up: calcium 132/2,295 vs placebo 121/2,294.
Participants	Pregnant nulliparas (45% black, 35% non-Hispanic white, 17% Hispanic white). Passed compliance test (took 75% of placebo over 6-14 days); BP 134/84 mmHg or less; urine protein dipstick negative or trace; 13-21 weeks pregnant.

CPEP 1997 (*Continued*)

	Exclusion criteria: taking medications; obstetric or pre-existing diseases or personal characteristics which could influence study end-points, absorption or metabolism of calcium; any risk associated with calcium supplementation, or compliance; elevated serum creatinine (1.0 mg per decilitre or more) or calcium (10.6 mg per decilitre or more); renal disease; haematuria; history or family history of urolithiasis; frequent use of calcium supplements or antacids. Of 11,959 women screened, 5,703 excluded initially and a further 1,667 after the compliance test. The remaining 4,589 women were enrolled.
Interventions	2 g/day elemental calcium as calcium carbonate, or placebo. Taken until delivery, development of pre-eclampsia or suspicion of urolithiasis. All women took 50 mg calcium per day as normal supplementation and were asked to drink 6 glasses of water per day. Compliance was 64% in the calcium group and 67% in the placebo group. 20% of women took > 90% of the allocated treatment.
Outcomes	Gestational hypertension (DBP sitting, fifth Korotkoff sound unless zero, 90 mmHg or more on 2 occasions, 4 hours-1 week apart); severe gestational hypertension (DBP 110 mmHg twice or treated, or complications); proteinuria (300 mg/24 hours or more, 1+ on 2 occasions 4 hours-1 week apart, 2+ or more, or protein/creatinine ratio 0.35 or more); pre-eclampsia (gestational hypertension + proteinuria within 7 days of each other); severe pre-eclampsia (50/2163 vs 59/2173); renal insufficiency (21/2163 vs 23/2173); urolithiasis (1/2163 vs 3/2173); prematurity (< 37 weeks); baby small for gestational age (124/2163 vs 105/2173); perinatal death. A limited follow up of mothers and infants found reduced systolic blood pressure at two years of age in the calcium supplementation group (Mean 95.4 mmHg, SD 7.6, n = 35 vs 100.2, 7.9, n = 18). The data have not been included in this review because the low and unequal follow-up rate (35 and 18 from 497 invited to participate) limit the reliability of the results.
Notes	Multicentre trial, 5 US university centres. Maternal outcomes reported as percentages of the whole number enrolled. In this review, denominators of 2,163 (calcium) and 2,173 (placebo) have been used. Neonatal outcomes in the report are based on live births (2134 and 2139). Addition of abortions and fetal deaths brings these numbers to 2156 and 2166. It is not clear why a discrepancy in numbers remains.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Crowther 1999

Methods	Central telephone randomisation, stratified by centre using variable blocks. Double-blind.
Participants	Inclusion criteria: Nulliparous women; Singleton pregnancy; < 24 weeks' gestation; Blood pressure < 140/90 mmHg; expected to give birth at a collaborating centre. Exclusion criteria: antihypertensive therapy; medical contraindication to calcium supplementation.

Crowther 1999 (*Continued*)

Interventions	Calcium carbonate 1.8 g daily or lactose placebo tablets, from 20-24 weeks till birth.
Outcomes	Primary: pregnancy-induced hypertension (diastolic blood pressure 90 mmHg or more on two consecutive occasions 4 hours apart, or 110 mmHg once; pre-eclampsia (as above plus proteinuria 0.3 g or more per 24 hours or 2+ protein or more on two random clean-catch urine samples); preterm birth (< 37 weeks). Secondary: severe pregnancy induced hypertension (diastolic blood pressure 110 or more on 2 occasions 4 hours apart, or 120 or more once); severe pre-eclampsia (as above plus proteinuria); very preterm birth (< 32 weeks; extremely preterm birth (< 28 weeks); maternal fetal and infant events after trial entry.
Notes	Five hospitals in Australia. August 1992 to December 1996. Estimated sample size 948. Trial stopped prematurely for financial reasons. 31% in the calcium group and 24% in the placebo group stopped taking the tablets during the trial. Analysis was by intention to treat.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

L-Jaramillo 1989

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

Risk of bias

Item	Authors' judgement	Description

L-Jaramillo 1989 (*Continued*)

Allocation concealment?	Unclear	D - Not used

L-Jaramillo 1990

Methods	Randomised, double-blind trial. Stated "Each patient was assigned independently in sequence", and "All women completed the study".
Participants	Healthy nulliparous women with positive roll-over test at 28-30 weeks' gestational age - judged at high risk for gestational hypertension.
Interventions	2,000 mg elemental calcium daily, from 28-32 weeks to delivery, vs placebo starch tablets.
Outcomes	Gestational hypertension (BP > 140/90 mmHg on 2 occasions 6 hours apart); proteinuria (300 mg/L); duration of pregnancy (calcium mean 39.2 (SD 1.2) vs placebo 37.4 (2.3) weeks); birthweight (2936 (396) vs 2685 (427) g).
Notes	Quito, Ecuador (altitude 2800 m). Large discrepancy in size of groups not accounted for.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

L-Jaramillo 1997

Methods	Prospective, randomised, double-blind, placebo controlled trial. 14 withdrawals after randomisation: 12 by change to another hospital or private medical doctor, 2 by non-compliance. 9/134 (6.7%) were from the calcium group and 5/140 (3.6%) from the placebo group.
Participants	Inclusion criteria: age < 17.5 years; nulliparous; first prenatal visit before 20 weeks' gestation; certain menstrual dates; residency in Quito for at least 1 year; BP =/< 120/80 mmHg; no underlying medical disorders; no drug, mineral or vitamin therapy. Average daily calcium intake in this population is 51% of the recommended dietary allowance.
Interventions	Elemental calcium 2 g daily as calcium carbonate from 20 weeks (n = 134), versus placebo tablets (n = 140).
Outcomes	Pre-eclampsia (BP > 140/90 mmHg on 2 occasions > 6 hours apart, and proteinuria > 300 mg/L (> 1+ on dipstick on 2 occasions 4-24 hours apart). BP recorded as mean of 2 measurements, 2 minutes apart, in the right arm, in the sitting position (1st and 5th Korotkoff sounds). Maternal serum ionised calcium at 38 weeks was calcium group mean 1.23, SD 0.02 mM vs placebo 1.16, 0.02; umbilical cord serum ionised calcium levels were calcium 1.44, 0.04 vs placebo 1,37, 0.03; gestational length was calcium 39.6, 0.4 versus placebo 38.7, 0.3.

L-Jaramillo 1997 (*Continued*)

Notes	Quito, Ecuador (altitude 2800 m). 1990 to 1995.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Niromanesh 2001

Methods	Double-blind, placebo controlled clinical trial. Women were "randomly assigned".	
Participants	Women at high risk for pre-eclampsia: positive 'roll-over' test and at least one risk factor for pre-eclampsia; 28-32 weeks' pregnant; blood pressure < 140/90 mmHg. Exclusion criteria: chronic medical conditions. Not defined as low- or adequate calcium intake (from table 1 dairy intake appears to be about 200 ml + 400 g per day).	
Interventions	Elemental calcium 2 g daily (500 mg 6-hourly) or placebo, coded by the pharmacy.	
Outcomes	Pre-eclampsia: an increase (30 mmHg) of systolic blood pressure above 14 mmHg and an increase (15 mmHg) of diastolic blood pressure above 90 mmHg, twice 4-6 hours apart, with proteinuria 1+; duration of pregnancy (39.5 SD 0.8 vs 37.7 SD 2.5 weeks); birthweight (3316 SD 308 vs 2764 SD 761 g); weekly maternal weight increase (no difference).	
Notes	No loss to follow up.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Purwar 1996

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

Purwar 1996 (*Continued*)

	Exclusion criteria: renal disease; collagen vascular disease; chronic hypertension; endocrinological disease; taking medication.
Interventions	Oral calcium containing 2 g elemental calcium daily (n = 103), compared with identical placebo tablets (n = 98), taken from 20 weeks.
Outcomes	Gestational hypertension (SBP > 140 mmHg and DBP > 90 mmHg, twice 6 hours apart) and pre-eclampsia (hypertension + proteinuria =/> 0.3 g/24 hours).
Notes	Nagpur, India.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

S-Ramos 1994

Methods	Double-blind placebo-controlled trial. Randomisation by computer-generated list. Outcome data entered before breaking the code. 4/33 allocated calcium lost to follow up.
Participants	Normotensive nulliparas; positive roll-over test (281/1065) and positive angiotensin II infusion test at 20-24 weeks' gestation (67/281). Exclusion criteria: factors increasing the risk of gestational hypertension, including renal disease, collagen vascular disease, diabetes mellitus, chronic hypertension, multifetal pregnancy.
Interventions	Calcium supplementation with 2 g per day elemental calcium as 500 mg calcium carbonate tablets, versus identical placebo tablets. Compliance checked with electronic pillboxes. Compliance was 79% vs 81%.
Outcomes	Gestational hypertension (BP at least 140/90 mmHg on 2 occasions 4-6 hours apart, on bedrest in hospital); pre-eclampsia (gestational hypertension + proteinuria: 1+ or 300 mg/24 hours); severe pre-eclampsia (pre-eclampsia plus one of BP at least 160 mmHg systolic or 110 mmHg diastolic; proteinuria at least 5 g/24 hours; oliguria < 400 ml per day; elevated liver enzymes; thrombocytopenia < 100,000/microlitre; pulmonary oedema; severe epigastric pain). Birthweight (calcium 3245 (SD 414) vs placebo 3035 (542) g); mean gestational ages (35.6 vs 34.4 weeks); 5 minute Apgar < 7 (1/29 vs 1/34); cord arterial pH (7.25 (0.07) vs 7.20 (0.07)); fetal growth impairment (2/29 vs 4/34).
Notes	Jacksonville, Florida, USA. University hospital serving low-income population.

Risk of bias

S-Ramos 1994 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Villar 1987

Methods	Double-blind, randomised controlled trial. Random numbers in closed envelopes.
Participants	Inclusion criteria: nulliparous or primiparous; known menstrual dates; age 18-30 years; singleton pregnancy; negative roll-over test. Exclusion criteria: underlying medical disorders. Mean calcium intake at 26 weeks was; calcium group: 1129 (SD 736) and placebo group 914 (478).
Interventions	Calcium carbonate 1.5 g (500 mg tablets) from 26 weeks' gestation vs placebo tablets. Women at John Hopkins Hospital also received vitamin preparations containing 200 mg calcium and 100 mg magnesium per day.
Outcomes	Weight gain in last trimester of pregnancy; BP increase; gestational hypertension.
Notes	Recruitment 1983-1985. 34 black women from John Hopkins Hospital, Baltimore, USA, 18 white women from Rosario, Argentina.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Villar 1990

Methods	Double-blind, randomised trial. Allocation by opaque envelopes, ordered by a computer-generated list of random numbers.
Participants	Pregnant women 17 years or younger; no underlying medical disorders; most were nulliparous with known last menstrual period and singleton pregnancy.
Interventions	2 g elemental calcium as 500 mg calcium carbonate tablets, vs placebo tablets. All women were prescribed prenatal vitamin tablets containing 200 mg calcium and 100 mg magnesium per day.
Outcomes	Preterm labour; preterm delivery (< 37 weeks); delivery 30-37 weeks; idiopathic prematurity; spontaneous prematurity; low birthweight (< 2500 g); postdates > 42 weeks (calcium 7.4 vs placebo 5.3%); impaired fetal growth (3.2 vs 3.2%); premature rupture of membranes (2.1 vs 1.0%); Apgar score < 8 at 5 minutes (4.4 vs 10.5%).

Villar 1990 (*Continued*)

Notes	John Hopkins Hospital, Baltimore, 1985-1988.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

WHO 2006

Methods	Double-blind, randomised trial. Randomisation stratified by centre, with computer generated blocks of 6-8. Allocation by consecutively numbered treatment packs containing calcium tablets or identical placebo. Treatment packs were prepared centrally.	
Participants	Populations with median daily calcium intake < 600 mg; Primiparous women less than 20 weeks pregnant. Exclusion criteria: renal disease or urolithiasis; parathyroid disease; blood pressure > 140 mmHg systolic or > 90 mmHg diastolic; history of hypertension; antihypertensive therapy; diuretic, digoxin, phenytoin or tetracycline treatment.	
Interventions	Chewable calcium carbonate tablets with 500 mg elemental calcium, 3 daily, or identical placebo, from enrolment till delivery.	
Outcomes	Primary outcomes: preeclampsia (blood pressure diastolic 90 mmHg or more, or systolic 140 mmHg or more, plus proteinuria 2+ on dipsticks or 300 mg per day; preterm birth (< 37 weeks). Secondary outcomes: severe pre-eclampsia (diastolic 110 mmHg or more or systolic 160 mmHg or more); early onset pre-eclampsia (< 32 weeks), pregnancy induced hypertension; eclampsia; placental abruption; birthweight < 2500 g; spontaneous preterm delivery; medically indicated preterm delivery; admission to neonatal ICU for > 2 days; fetal, neonatal and perinatal mortality (before discharge from hospital).	
Notes	Multicentre trial in Argentina, Egypt, India, Peru, South Africa and Vietnam. 14,362 women screened, 8325 randomised. Exclusions: 6 calcium (4 not pregnant, 2 lost before treatment started) and 7 placebo (5 not pregnant, 2 lost before treatment started). Loss to follow up: 143 and 155 in calcium and placebo group respectively (some data available on women not followed up to delivery). Treatment compliance 84.5% and 86.2% respectively. Baseline characteristics well matched.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

BP: blood pressure
CI: confidence interval
DBP: diastolic blood pressure
RR: relative risk
SBP: systolic blood pressure

SD: standard deviation
SEM: standard error of the mean
vs: versus

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

Almirante 1998	The method of allocation is not clear from the abstract.
August 2002	Excluded pending full report of results. Inadequate data in abstracts for inclusion.
Belizan 1983	N = 36. No clinically important outcomes presented in format suitable for inclusion in this review. Participants: healthy, 20-35 years, singleton pregnancy. Intervention: calcium 1 g (n = 11), calcium 2 g (n = 11) or placebo (n = 14). Outcomes: DBP 20-24 weeks, and in the third trimester. Study design: randomised, no further information.
Boggess 1997	N = 23. After randomisation, 5/23 (22%) were excluded. Participants: 18-35 years. Excluded if BP > 140/90 mmHg at 24 weeks; smokers; illicit drug use; multiple pregnancy; cardiovascular renal or endocrine disease; hypertension in previous pregnancy; calcium supplementation > 200-250 mg elemental calcium. Intervention: oral calcium carbonate 1.5 g/day for 6 weeks from 28-31 weeks, or placebo tablets. All had 200-250 mg calcium in standard prenatal vitamin-mineral preparations. Outcomes: gestational hypertension (BP at least 140.90 mmHg on 2 occasions, 6 hours apart); pre-eclampsia (gestational hypertension plus at least 1+ proteinuria) Study design: randomised trial. Randomisation schedule in balanced blocks of 10.
Chames 2002	Excluded pending publication of full report. No relevant clinical outcomes reported in the abstract. No difference found in blood lead levels between women receiving calcium 1000 mg daily from 13-19 weeks (n = 24) or placebo (n = 26).
Cong 1995	Beijing Obstetrics and Gynecology Hospital. Three studies reported, but due to serious uncertainty about the method of randomisation in these studies, all have been excluded from this review. Study 1: calcium 120 mg vs 480 mg vs no calcium. Study 2: calcium 1 g vs 2 g vs no calcium. Study 3: calcium 2 g vs no calcium.
Felix 1991	Excluded as allocation was by alternation, not random. 14 women received calcium supplementation and 11 received placebo. No women developed hypertension or pre-eclampsia. The production of 6-keto-prostaglandin F1alpha by umbilical arteries was similar between groups.
Herrera 1998	Excluded because the intervention was a combination of calcium and linoleic acid.

(*Continued*)

Kawasaki 1985	N = 94. Not a randomised trial. Interventions: calcium L-aspartate 600 mg/day from 20 weeks to delivery (n = 22) vs no supplementation (n = 72). Outcomes: pregnancy-induced hypertension.
Knight 1992	Excluded because no clinically relevant outcomes reported, placebo not used, and participants not followed till delivery. Normotensive (n = 30 and hypertensive (BP 140/85 mmHg or more, n = 20) nulliparous women "randomly allocated" to receive calcium 1 gram from about 12 weeks to 32 weeks, or a control group. Follow up continued to 36 weeks. Mean diastolic blood pressure reduced in the hypertensive group receiving calcium.
Lavin 1986	Planned trial of calcium versus placebo in women with a positive roll-over test at 28-32 weeks. Trial apparently cancelled.
Marya 1987	N = 400. The method for allocating women to the two groups was not clear from the report. Additional information obtained from the first author indicated that alternate allocation was used. Interventions: calcium 375 mg per day plus vitamin D 1200 IU per day from 20-24 weeks onward, and no supplementation. Outcomes: 'toxaemia'.
Montanaro 1990	N = 170. No placebo. Participants: normotensive at 24 weeks' pregnancy. Interventions: calcium 2 g/day from 24 weeks to delivery. Outcomes: pregnancy induced hypertension, pre-eclampsia. Study design: "randomised, single-blinded trial".
Prada 2001	Excluded pending publication of full report. Abstract does not include outcomes specified for this review. Mean blood pressure was reduced in adolescents receiving calcium supplementation 1000 mg daily (n = 62) compared with placebo (n = 62). Not clear whether participants in this report include participants from Prada 2002.
Prada 2002	Excluded pending publication of full report. Abstract does not include outcomes specified for this review. Mean blood pressure was similar in adolescents and women with twin pregnancy receiving calcium supplementation 1000 mg daily (n = 94) compared with placebo (n = 93). Not clear whether participants in this report include participants from Prada 2001.
Raman 1978	N = 273. Allocation was by strict rotation, a quasi-randomised trial. Supplementation with < 1 g/day.
Repke 1989	N = 255. Presented as abstract only. No clinical data available. Interventions: calcium 2 g/day vs placebo, after 20 weeks of pregnancy. Study design: 'randomised clinical trial'.
Rogers 1999	Excluded because: (1) randomisation performed "using five unsealed envelopes"; unequal group numbers suggested that 'something went wrong with the randomisation process'; (2) no placebo used; (3) initial calcium dose 600 mg per day (1200 mg per day after 32 weeks); (4) 10% loss to follow up. Hypertension alone occurred in 21/144 women who received calcium compared with 18/75 controls; pre-eclampsia in 8/144 vs 7/75 respectively.

(*Continued*)

S-Ramos 1995	N = 75. Excluded because calcium used for treatment of women with pre-eclampsia rather than prevention. Participants: nulliparous, gestation 24-36 weeks; mild pre-eclampsia (BP 140/90-160/100, proteinuria at least 300 mg/day). Interventions: calcium 2 g/day elemental calcium (four tablets of calcium carbonate 1250 mg), versus matching placebo. Outcomes: initial and last BP and biochemical markers; preterm delivery; caesarean section; severe pre-eclampsia; gestation at delivery; birthweight; Apgar < 7 at 1 minute and 5 minutes; cord arterial pH < 7.16; fetal growth restriction; perinatal death. Study design: double-blind, placebo-controlled study using a computer-generated random number list.
Suzuki 1996	N = 152. Not a randomised trial. Interventions: calcium 1 g/day from 20 weeks vs no calcium. Outcomes: pre-eclampsia, gestational hypertension.
Taherian 2002	Inclusion citeria not met: not placebo-controlled, calcium dose < 1 g. Three-way comparison between calcium 500 mg, low-dose aspirin and no treatment. Pre-eclampsia diagnosed in 13/330, 15/330 and 33/330 respectively.
Tamas 1997	Study of treatment of gestational hypertension, not prevention, using the drug dobesilate calcium, not calcium supplementation.
Wanchu 2001	No placebo used. 120 consecutive nulliparous women less than 20 weeks pregnant "randomly assigned" to receive 2 g elemental calcium daily, or no treatment. Analysis restricted to 100 women who "completed the protocol". Mild pre-eclampsia occurred in 9/50 vs 6/50 and severe pre-eclampsia in 0/50 vs 2/50 study vs control groups respectively.

BP: blood pressure
DBP: diastolic blood pressure
IU: international unit
vs: versus

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

Mahomed 1998

Trial name or title	Calcium supplementation for the prevention of pregnancy induced hypertension and preterm labour in twin pregnancies: a randomised controlled trial.
Methods	
Participants	Women with twin pregnancy.

Mahomed 1998 (*Continued*)

Interventions	Calcium solution (1 g elemental calcium per 5 ml).
Outcomes	Pregnancy-induced hypertension, preterm labour, perinatal mortality and short-term morbidity, maternal morbidity.
Starting date	Not stated.
Contact information	Prof K Mahomed.
Notes	Sample size 400 per group.

DATA AND ANALYSES

Comparison 1. Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without proteinuria)	11	14946	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.57, 0.86]
1.1 Adequate calcium diet	4	5022	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 0.99]
1.2 Low calcium diet	6	9894	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.76]
1.3 Dietary calcium not specified	1	30	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.45]
2 Pre-eclampsia	12	15206	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.69]
2.1 Adequate calcium diet	4	5022	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.20]
2.2 Low calcium diet	7	10154	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.18, 0.70]
2.3 Dietary calcium not specified	1	30	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.02]
3 Maternal death/serious morbidity	4	9732	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.97]
3.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Low calcium diet	4	9732	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.97]
4 Placental abruption	5	14309	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.34]
4.1 Adequate calcium diet	3	4830	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.39, 1.68]
4.3 Low calcium diet	2	9479	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.51, 1.56]
5 Caesarean section	7	14710	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.01]
5.1 Adequate calcium diet	3	4981	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
5.3 Low calcium diet	4	9729	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.87, 1.03]
6 Proteinuria (gestational with no proteinuria	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.26]
6.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.26]
7 Severe pre-eclamsia	1	8302	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.15]
7.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Low calcium diet	1	8302	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.15]
8 Eclampsia	2	12901	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.41, 1.27]
8.1 Adequate calcium diet	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.25, 3.99]
8.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.37, 1.26]
9 HELLP syndrome	2	12901	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.05, 6.82]
9.1 Adequate calcium diet	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.73, 16.82]
9.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.70, 7.32]
10 ICU admission	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
10.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
11 Maternal death	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.39]
11.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 Low calcium diet	1	8312	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.39]
13 Preterm birth	10	14751	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.03]
13.1 Adequate calcium diet	4	5033	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.26, 1.33]
13.3 Low calcium diet	6	9718	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.02]

14 Birthweight < 2500 g	8	14359	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.68, 1.03]
14.1 Adequate calcium diet	4	5033	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.31, 1.13]
14.3 Low calcium diet	4	9326	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.08]
15 Neonate small-for-gestational age as defined by trial authors	3	13091	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.88, 1.37]
15.1 Adequate calcium diet	1	4589	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.92, 1.52]
15.3 Low calcium diet	2	8502	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.59, 1.38]
16 Admission to neonatal intensive care unit	4	13406	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
16.1 Adequate calcium diet	1	4336	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.95, 1.26]
16.3 Low calcium diet	3	9070	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.19]
18 Stillbirth or death before discharge from hospital	10	15141	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
18.1 Adequate calcium diet	4	5033	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.66, 1.90]
18.3 Low calcium diet	6	10108	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.06]
21 Childhood systolic blood pressure > 95th percentile	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.91]
21.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.3 Low calcium diet	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.91]
22 Childhood diastolic blood pressure > 95th percentile	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]
22.1 Adequate calcium diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22.3 Low calcium diet	1	514	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.50, 1.31]

Comparison 2. Routine calcium supplementation in pregnancy by hypertension risk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without proteinuria)	11	14946	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.57, 0.86]
1.1 Low-risk women	7	14619	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.64, 0.95]
1.2 High-risk women	4	327	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 0.97]
2 Pre-eclampsia	12	15206	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.69]
2.1 Low-risk women	7	14619	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.49, 0.94]
2.2 High-risk women	5	587	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.12, 0.42]
13 Preterm birth	10	14751	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.03]
13.1 Low-risk women	6	14183	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.12]
13.2 High-risk women	4	568	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.24, 0.83]
16 Admission to neonatal intensive care unit	4	13406	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
16.1 Low-risk women	3	13343	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.19]
16.2 High-risk women	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.03, 2.48]
18 Stillbirth or death before discharge from hospital	10	15141	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
18.1 Low-risk women	7	14629	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
18.2 High-risk women	3	512	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 9.20]

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High blood pressure (with or without proteinuria)	11	14946	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.57, 0.86]
1.1 Studies with < 400 participants	7	675	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.21, 0.68]
1.2 Studies with =/> 400 participants	4	14271	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
2 Pre-eclampsia	12	15206	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.69]
2.1 Studies with < 400 participants	8	935	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.12, 0.36]
2.2 Studies with =/> 400 participants	4	14271	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]
13 Preterm birth	10	14751	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.64, 1.03]
13.1 Studies with < 400 participants	6	810	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.24, 0.76]
13.2 Studies with =/> 400 participants	4	13941	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.76, 1.13]
16 Admission to neonatal intensive care unit	4	13406	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.18]
16.1 Studies with < 400 participants	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.03, 2.48]
16.2 Studies with =/> 400 participants	3	13343	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.19]
18 Stillbirth or death before discharge from hospital	10	15141	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
18.1 Studies with < 400 participants	6	846	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 9.20]
18.2 Studies with =/> 400 participants	4	14295	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]

Comparison 4. Routine calcium supplementation in pregnancy by baseline dietary calcium and study sample size

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Pre-eclampsia	12	15206	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.69]
2.1 Adequate calcium/small study	2	230	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.04, 1.50]
2.2 Adequate calcium/large study	2	4792	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.33, 1.46]
2.3 Low calcium/small study	5	675	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.12, 0.38]
2.4 Low calcium/large study	2	9479	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.09]

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

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

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

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

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate calcium diet					
Villar 1987	1/25	3/27		0.8 %	0.36 [0.04, 3.24]
Villar 1990	3/90	8/88		2.2 %	0.37 [0.10, 1.34]
Crowther 1999	34/227	38/229		11.4 %	0.90 [0.59, 1.38]
CPEP 1997	509/2163	565/2173		21.2 %	0.91 [0.82, 1.00]
Subtotal (95% CI)	**2505**	**2517**		**35.6 %**	**0.90 [0.81, 0.99]**
Total events: 547 (Calcium), 614 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.53, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.09 (P = 0.036)					
2 Low calcium diet					
L-Jaramillo 1990	3/22	24/34		3.1 %	0.19 [0.07, 0.57]
S-Ramos 1994	9/29	22/34		7.7 %	0.48 [0.26, 0.87]
L-Jaramillo 1989	2/55	12/51		1.8 %	0.15 [0.04, 0.66]
Purwar 1996	8/97	27/93		5.7 %	0.28 [0.14, 0.59]
Belizan 1991	57/579	87/588		14.6 %	0.67 [0.49, 0.91]
WHO 2006	613/4151	645/4161		21.3 %	0.95 [0.86, 1.05]
Subtotal (95% CI)	**4933**	**4961**		**54.2 %**	**0.47 [0.29, 0.76]**
Total events: 692 (Calcium), 817 (Placebo)					
Heterogeneity: Tau^2 = 0.24; Chi^2 = 31.70, df = 5 (P<0.00001); I^2 =84%					
Test for overall effect: Z = 3.11 (P = 0.0019)					
3 Dietary calcium not specified					
Niromanesh 2001	10/15	11/15		10.2 %	0.91 [0.57, 1.45]
Subtotal (95% CI)	**15**	**15**		**10.2 %**	**0.91 [0.57, 1.45]**
Total events: 10 (Calcium), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					
Total (95% CI)	**7453**	**7493**		**100.0 %**	**0.70 [0.57, 0.86]**
Total events: 1249 (Calcium), 1442 (Placebo)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 34.43, df = 10 (P = 0.00016); I^2 =71%					
Test for overall effect: Z = 3.43 (P = 0.00060)					

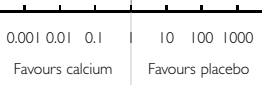
Analysis 1.2. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 2 Pre-eclampsia.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 2 Pre-eclampsia

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate calcium diet					
Villar 1987	1/25	3/27		2.5 %	0.36 [0.04, 3.24]
Villar 1990	0/90	3/88		1.5 %	0.14 [0.01, 2.67]
Crowther 1999	10/227	23/229		11.9 %	0.44 [0.21, 0.90]
CPEP 1997	158/2163	168/2173		19.9 %	0.94 [0.77, 1.16]
Subtotal (95% CI)	**2505**	**2517**		**35.8 %**	**0.62 [0.32, 1.20]**
Total events: 169 (Calcium), 197 (Placebo)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 6.20, df = 3 (P = 0.10); I^2 =52%					
Test for overall effect: Z = 1.43 (P = 0.15)					
2 Low calcium diet					
L-Jaramillo 1990	0/22	8/34		1.6 %	0.09 [0.01, 1.48]
S-Ramos 1994	4/29	15/34		8.6 %	0.31 [0.12, 0.84]
L-Jaramillo 1989	2/55	12/51		5.1 %	0.15 [0.04, 0.66]
Purwar 1996	2/97	11/93		4.9 %	0.17 [0.04, 0.77]
L-Jaramillo 1997	4/125	21/135		8.0 %	0.21 [0.07, 0.58]
Belizan 1991	15/579	23/588		13.1 %	0.66 [0.35, 1.26]
WHO 2006	171/4151	186/4161		19.9 %	0.92 [0.75, 1.13]
Subtotal (95% CI)	**5058**	**5096**		**61.2 %**	**0.36 [0.18, 0.70]**
Total events: 198 (Calcium), 276 (Placebo)					
Heterogeneity: Tau^2 = 0.48; Chi^2 = 23.85, df = 6 (P = 0.00056); I^2 =75%					
Test for overall effect: Z = 3.03 (P = 0.0024)					
3 Dietary calcium not specified					
Niromanesh 2001	1/15	7/15		3.1 %	0.14 [0.02, 1.02]
Subtotal (95% CI)	**15**	**15**		**3.1 %**	**0.14 [0.02, 1.02]**
Total events: 1 (Calcium), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.053)					
Total (95% CI)	**7578**	**7628**		**100.0 %**	**0.48 [0.33, 0.69]**
Total events: 368 (Calcium), 480 (Placebo)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 33.90, df = 11 (P = 0.00038); I^2 =68%					
Test for overall effect: Z = 3.88 (P = 0.00010)					



Analysis 1.3. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 3 Maternal death/serious morbidity.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 3 Maternal death/serious morbidity

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

Analysis 1.4. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 4 Placental abruption.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 4 Placental abruption

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet				
Villar 1987	0/25	0/27		0.0 [0.0, 0.0]
Villar 1990	0/94	0/95		0.0 [0.0, 0.0]
CPEP 1997	13/2295	16/2294		0.81 [0.39, 1.68]
Subtotal (95% CI)	**2414**	**2416**		**0.81 [0.39, 1.68]**
Total events: 13 (Calcium), 16 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.56 (P = 0.58)				
3 Low calcium diet				
Belizan 1991	6/579	4/588		1.52 [0.43, 5.37]
WHO 2006	17/4151	22/4161		0.77 [0.41, 1.46]
Subtotal (95% CI)	**4730**	**4749**		**0.89 [0.51, 1.56]**
Total events: 23 (Calcium), 26 (Placebo)				
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² =0.0%				
Test for overall effect: Z = 0.41 (P = 0.68)				
Total (95% CI)	**7144**	**7165**		**0.86 [0.55, 1.34]**
Total events: 36 (Calcium), 42 (Placebo)				
Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² =0.0%				
Test for overall effect: Z = 0.67 (P = 0.50)				

Analysis 1.5. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 5 Caesarean section.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 5 Caesarean section

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Villar 1990	16/94	17/95		1.2 %	0.95 [0.51, 1.77]
Crowther 1999	46/227	46/229		3.3 %	1.01 [0.70, 1.45]
CPEP 1997	366/2163	390/2173		28.1 %	0.94 [0.83, 1.07]
Subtotal (95% CI)	**2484**	**2497**		**32.7 %**	**0.95 [0.84, 1.07]**
Total events: 428 (Calcium), 453 (Placebo)					
Heterogeneity: Chi^2 = 0.12, df = 2 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.84 (P = 0.40)					
3 Low calcium diet					
S-Ramos 1994	1/29	6/34		0.4 %	0.20 [0.02, 1.53]
Purwar 1996	6/97	7/93		0.5 %	0.82 [0.29, 2.35]
Belizan 1991	60/544	66/554		4.7 %	0.93 [0.67, 1.29]
WHO 2006	809/4181	854/4197		61.7 %	0.95 [0.87, 1.04]
Subtotal (95% CI)	**4851**	**4878**		**67.3 %**	**0.94 [0.87, 1.03]**
Total events: 876 (Calcium), 933 (Placebo)					
Heterogeneity: Chi^2 = 2.36, df = 3 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 1.37 (P = 0.17)					
Total (95% CI)	**7335**	**7375**		**100.0 %**	**0.95 [0.88, 1.01]**
Total events: 1304 (Calcium), 1386 (Placebo)					
Heterogeneity: Chi^2 = 2.48, df = 6 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 1.60 (P = 0.11)					

Analysis 1.6. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 6 Proteinuria (gestational with no proteinuria.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 6 Proteinuria (gestational with no proteinuria

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low calcium diet					
WHO 2006	201/4151	194/4161		100.0 %	1.04 [0.86, 1.26]
Subtotal (95% CI)	**4151**	**4161**		**100.0 %**	**1.04 [0.86, 1.26]**
Total events: 201 (Calcium), 194 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					
Total (95% CI)	**4151**	**4161**		**100.0 %**	**1.04 [0.86, 1.26]**
Total events: 201 (Calcium), 194 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					

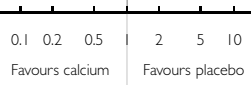
Analysis 1.7. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 7 Severe pre-eclamsia.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 7 Severe pre-eclamsia

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low calcium diet					
WHO 2006	35/4151	47/4151		100.0 %	0.74 [0.48, 1.15]
Subtotal (95% CI)	**4151**	**4151**		**100.0 %**	**0.74 [0.48, 1.15]**
Total events: 35 (Calcium), 47 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
Total (95% CI)	**4151**	**4151**		**100.0 %**	**0.74 [0.48, 1.15]**
Total events: 35 (Calcium), 47 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					

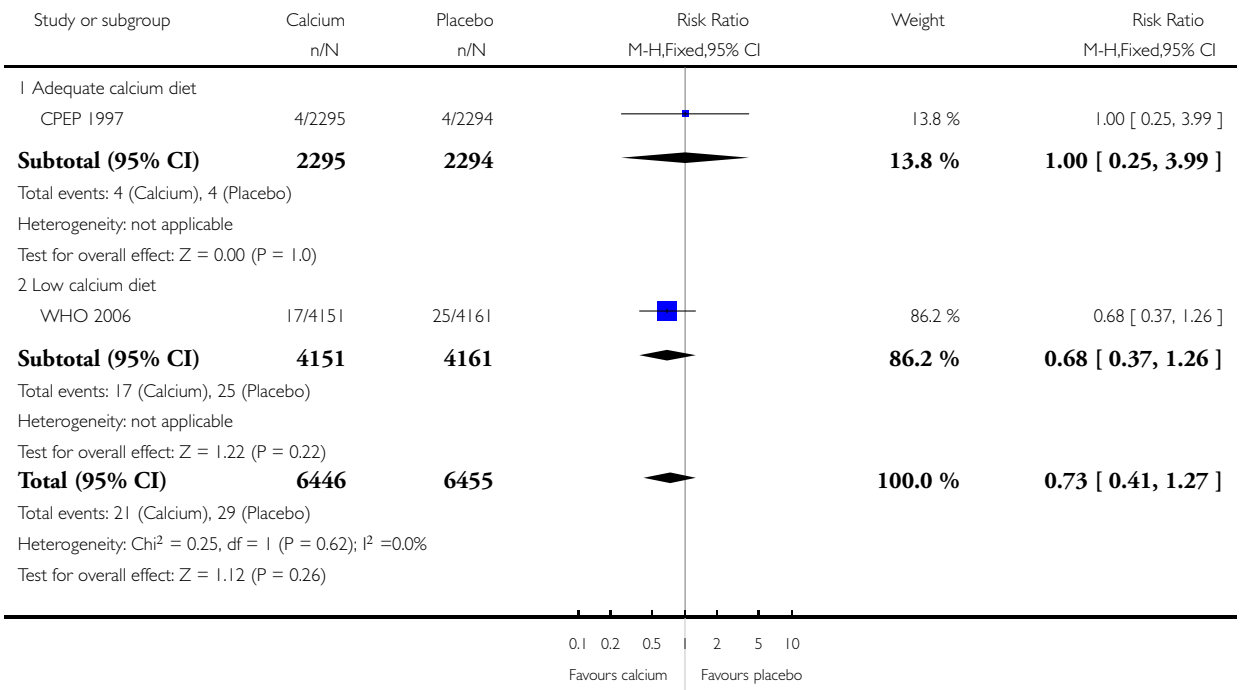


Analysis 1.8. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 8 Eclampsia.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 8 Eclampsia



Analysis 1.9. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 9 HELLP syndrome.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 9 HELLP syndrome

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
CPEP 1997	7/2295	2/2294		33.4 %	3.50 [0.73, 16.82]
Subtotal (95% CI)	**2295**	**2294**		**33.4 %**	**3.50 [0.73, 16.82]**
Total events: 7 (Calcium), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.56 (P = 0.12)					
2 Low calcium diet					
WHO 2006	9/4151	4/4161		66.6 %	2.26 [0.70, 7.32]
Subtotal (95% CI)	**4151**	**4161**		**66.6 %**	**2.26 [0.70, 7.32]**
Total events: 9 (Calcium), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					
Total (95% CI)	**6446**	**6455**		**100.0 %**	**2.67 [1.05, 6.82]**
Total events: 16 (Calcium), 6 (Placebo)					
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 2.05 (P = 0.040)					

Analysis 1.10. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 10 ICU admission.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 10 ICU admission

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low calcium diet					
WHO 2006	116/4151	138/4161		100.0 %	0.84 [0.66, 1.07]
Subtotal (95% CI)	**4151**	**4161**		**100.0 %**	**0.84 [0.66, 1.07]**
Total events: 116 (Calcium), 138 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
Total (95% CI)	**4151**	**4161**		**100.0 %**	**0.84 [0.66, 1.07]**
Total events: 116 (Calcium), 138 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					

Analysis 1.11. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 11 Maternal death.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 11 Maternal death

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Low calcium diet					
WHO 2006	1/4151	6/4161		100.0 %	0.17 [0.02, 1.39]
Subtotal (95% CI)	**4151**	**4161**		**100.0 %**	**0.17 [0.02, 1.39]**
Total events: 1 (Calcium), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.098)					
Total (95% CI)	**4151**	**4161**		**100.0 %**	**0.17 [0.02, 1.39]**
Total events: 1 (Calcium), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.098)					

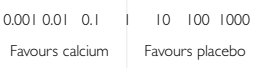
Analysis 1.13. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 13 Preterm birth.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 13 Preterm birth

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Adequate calcium diet				
Villar 1987	0/25	0/27		0.0 [0.0, 0.0]
Villar 1990	7/94	20/95		0.35 [0.16, 0.80]
Crowther 1999	10/227	23/229		0.44 [0.21, 0.90]
CPEP 1997	248/2163	229/2173		1.09 [0.92, 1.29]
Subtotal (95% CI)	**2509**	**2524**		**0.59 [0.26, 1.33]**
Total events: 265 (Calcium), 272 (Placebo)				
Heterogeneity: Tau^2 = 0.42; Chi^2 = 12.31, df = 2 (P = 0.002); I^2 =84%				
Test for overall effect: Z = 1.26 (P = 0.21)				
3 Low calcium diet				
L-Jaramillo 1990	0/22	4/34		0.17 [0.01, 2.99]
S-Ramos 1994	5/29	8/34		0.73 [0.27, 1.99]
Purwar 1996	2/97	6/93		0.32 [0.07, 1.54]
L-Jaramillo 1997	0/125	0/135		0.0 [0.0, 0.0]
Belizan 1991	33/527	37/542		0.92 [0.58, 1.44]
WHO 2006	398/4038	436/4042		0.91 [0.80, 1.04]
Subtotal (95% CI)	**4838**	**4880**		**0.90 [0.80, 1.02]**
Total events: 438 (Calcium), 491 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.19, df = 4 (P = 0.53); I^2 =0.0%				
Test for overall effect: Z = 1.64 (P = 0.10)				
Total (95% CI)	**7347**	**7404**		**0.81 [0.64, 1.03]**
Total events: 703 (Calcium), 763 (Placebo)				
Heterogeneity: Tau^2 = 0.04; Chi^2 = 16.36, df = 7 (P = 0.02); I^2 =57%				
Test for overall effect: Z = 1.72 (P = 0.086)				



Analysis 1.14. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 14 Birthweight < 2500 g.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 14 Birthweight < 2500 g

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Adequate calcium diet				
Villar 1987	0/25	0/27		0.0 [0.0, 0.0]
Villar 1990	9/94	20/95		0.45 [0.22, 0.95]
Crowther 1999	6/227	17/229		0.36 [0.14, 0.89]
CPEP 1997	188/2163	205/2173		0.92 [0.76, 1.11]
Subtotal (95% CI)	**2509**	**2524**		**0.59 [0.31, 1.13]**
Total events: 203 (Calcium), 242 (Placebo)				
Heterogeneity: Tau^2 = 0.23; Chi^2 = 7.00, df = 2 (P = 0.03); I^2 =71%				
Test for overall effect: Z = 1.58 (P = 0.11)				
3 Low calcium diet				
L-Jaramillo 1989	0/49	0/43		0.0 [0.0, 0.0]
L-Jaramillo 1997	0/125	0/135		0.0 [0.0, 0.0]
Belizan 1991	31/547	41/559		0.77 [0.49, 1.21]
WHO 2006	512/3930	524/3938		0.98 [0.87, 1.10]
Subtotal (95% CI)	**4651**	**4675**		**0.97 [0.86, 1.08]**
Total events: 543 (Calcium), 565 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.99, df = 1 (P = 0.32); I^2 =0.0%				
Test for overall effect: Z = 0.63 (P = 0.53)				
Total (95% CI)	**7160**	**7199**		**0.84 [0.68, 1.03]**
Total events: 746 (Calcium), 807 (Placebo)				
Heterogeneity: Tau^2 = 0.03; Chi^2 = 9.36, df = 4 (P = 0.05); I^2 =57%				
Test for overall effect: Z = 1.66 (P = 0.097)				

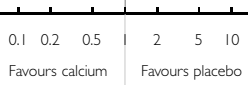
Analysis 1.15. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 15 Neonate small-for-gestational age as defined by trial authors.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 15 Neonate small-for-gestational age as defined by trial authors

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
CPEP 1997	124/2295	105/2294		70.4 %	1.18 [0.92, 1.52]
Subtotal (95% CI)	**2295**	**2294**		**70.4 %**	**1.18 [0.92, 1.52]**
Total events: 124 (Calcium), 105 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
3 Low calcium diet					
Purwar 1996	6/97	8/93		5.5 %	0.72 [0.26, 1.99]
WHO 2006	34/4151	36/4161		24.1 %	0.95 [0.59, 1.51]
Subtotal (95% CI)	**4248**	**4254**		**29.6 %**	**0.90 [0.59, 1.38]**
Total events: 40 (Calcium), 44 (Placebo)					
Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.46 (P = 0.64)					
Total (95% CI)	**6543**	**6548**		**100.0 %**	**1.10 [0.88, 1.37]**
Total events: 164 (Calcium), 149 (Placebo)					
Heterogeneity: Chi^2 = 1.36, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.85 (P = 0.39)					



Analysis 1.16. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 16 Admission to neonatal intensive care unit.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 16 Admission to neonatal intensive care unit

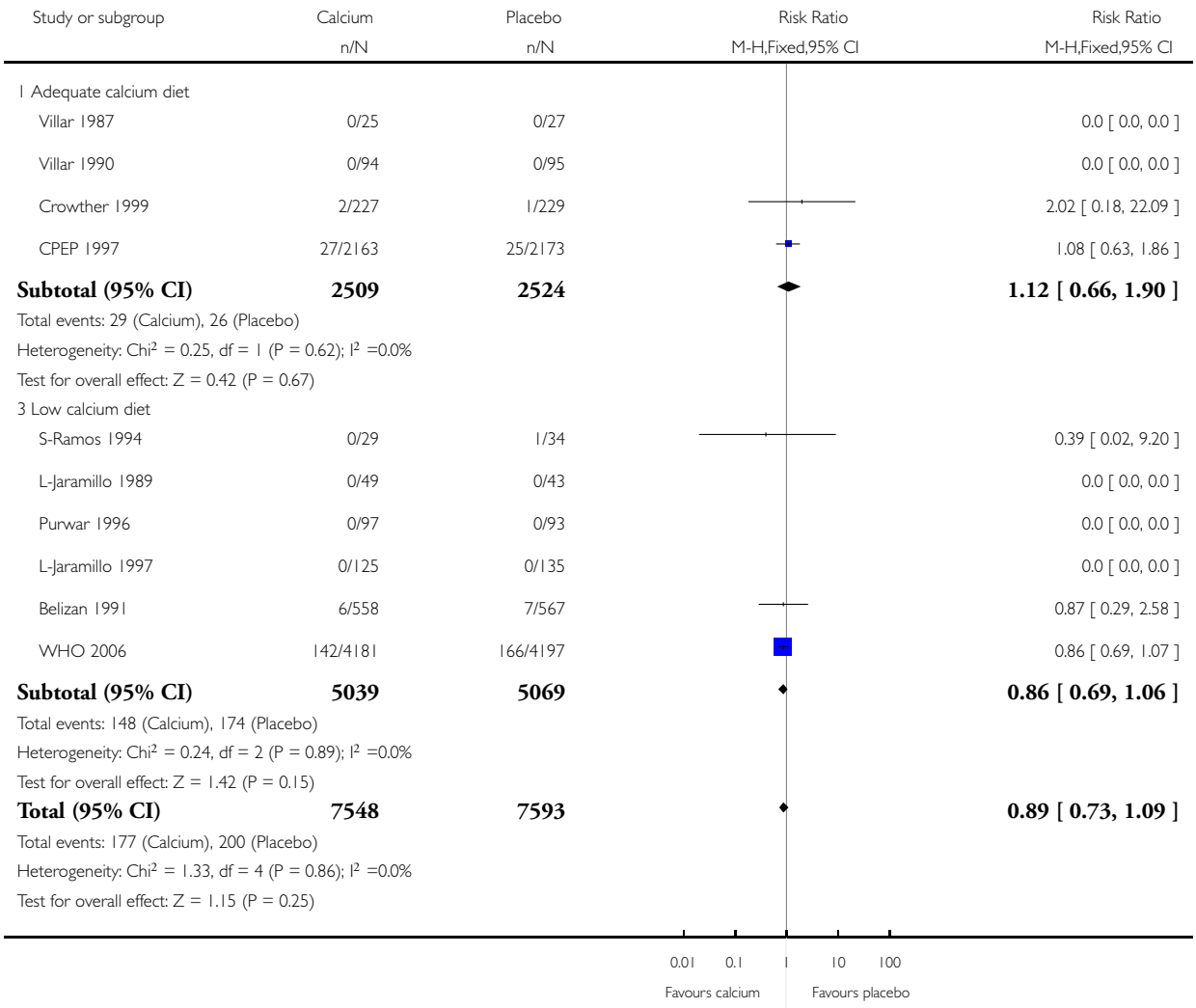
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
CPEP 1997	343/2163	315/2173		62.2 %	1.09 [0.95, 1.26]
Subtotal (95% CI)	**2163**	**2173**		**62.2 %**	**1.09 [0.95, 1.26]**
Total events: 343 (Calcium), 315 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
3 Low calcium diet					
S-Ramos 1994	1/29	4/34		0.7 %	0.29 [0.03, 2.48]
Belizan 1991	72/544	65/554		12.7 %	1.13 [0.82, 1.54]
WHO 2006	114/3953	123/3956		24.3 %	0.93 [0.72, 1.19]
Subtotal (95% CI)	**4526**	**4544**		**37.8 %**	**0.98 [0.81, 1.19]**
Total events: 187 (Calcium), 192 (Placebo)					
Heterogeneity: Chi^2 = 2.18, df = 2 (P = 0.34); I^2 =8%					
Test for overall effect: Z = 0.17 (P = 0.86)					
Total (95% CI)	**6689**	**6717**		**100.0 %**	**1.05 [0.94, 1.18]**
Total events: 530 (Calcium), 507 (Placebo)					
Heterogeneity: Chi^2 = 2.83, df = 3 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.87 (P = 0.38)					

Analysis 1.18. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 18 Stillbirth or death before discharge from hospital.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 18 Stillbirth or death before discharge from hospital



Analysis 1.21. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 21 Childhood systolic blood pressure > 95th percentile.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 21 Childhood systolic blood pressure > 95th percentile

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Low calcium diet					
Belizan 1991	29/254	50/260		100.0 %	0.59 [0.39, 0.91]
Subtotal (95% CI)	**254**	**260**		**100.0 %**	**0.59 [0.39, 0.91]**
Total events: 29 (Calcium), 50 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
Total (95% CI)	**254**	**260**		**100.0 %**	**0.59 [0.39, 0.91]**
Total events: 29 (Calcium), 50 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					

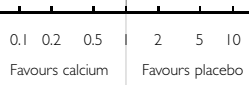
Analysis 1.22. Comparison 1 Routine calcium supplementation in pregnancy by baseline dietary calcium, Outcome 22 Childhood diastolic blood pressure > 95th percentile.

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

Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 22 Childhood diastolic blood pressure > 95th percentile

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adequate calcium diet					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Calcium), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Low calcium diet					
Belizan 1991	26/254	33/260		100.0 %	0.81 [0.50, 1.31]
Subtotal (95% CI)	**254**	**260**		**100.0 %**	**0.81 [0.50, 1.31]**
Total events: 26 (Calcium), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					
Total (95% CI)	**254**	**260**		**100.0 %**	**0.81 [0.50, 1.31]**
Total events: 26 (Calcium), 33 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					



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

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

Comparison: 2 Routine calcium supplementation in pregnancy by hypertension risk

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

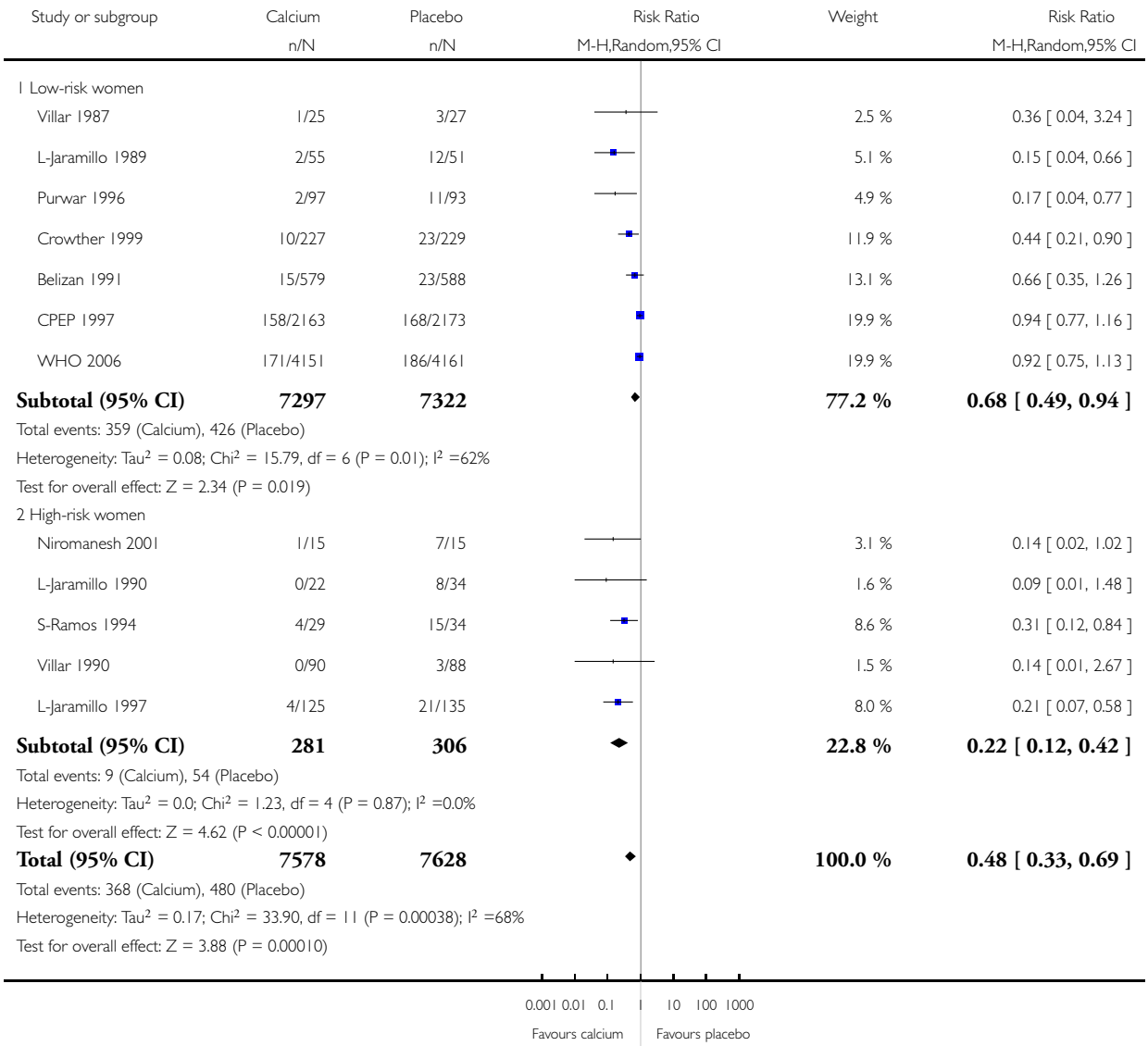
Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-risk women					
Villar 1987	1/25	3/27		0.8 %	0.36 [0.04, 3.24]
L-Jaramillo 1989	2/55	12/51		1.8 %	0.15 [0.04, 0.66]
Purwar 1996	8/97	27/93		5.7 %	0.28 [0.14, 0.59]
Crowther 1999	34/227	38/229		11.4 %	0.90 [0.59, 1.38]
Belizan 1991	57/579	87/588		14.6 %	0.67 [0.49, 0.91]
CPEP 1997	509/2163	565/2173		21.2 %	0.91 [0.82, 1.00]
WHO 2006	613/4151	645/4161		21.3 %	0.95 [0.86, 1.05]
Subtotal (95% CI)	**7297**	**7322**		**76.8 %**	**0.78 [0.64, 0.95]**
Total events: 1224 (Calcium), 1377 (Placebo)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 20.61$, df = 6 (P = 0.002); $I^2 = 71\%$					
Test for overall effect: Z = 2.45 (P = 0.014)					
2 High-risk women					
Niromanesh 2001	10/15	11/15		10.2 %	0.91 [0.57, 1.45]
L-Jaramillo 1990	3/22	24/34		3.1 %	0.19 [0.07, 0.57]
S-Ramos 1994	9/29	22/34		7.7 %	0.48 [0.26, 0.87]
Villar 1990	3/90	8/88		2.2 %	0.37 [0.10, 1.34]
Subtotal (95% CI)	**156**	**171**		**23.2 %**	**0.47 [0.22, 0.97]**
Total events: 25 (Calcium), 65 (Placebo)					
Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 11.01$, df = 3 (P = 0.01); $I^2 = 73\%$					
Test for overall effect: Z = 2.03 (P = 0.042)					
Total (95% CI)	**7453**	**7493**		**100.0 %**	**0.70 [0.57, 0.86]**
Total events: 1249 (Calcium), 1442 (Placebo)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 34.43$, df = 10 (P = 0.00016); $I^2 = 71\%$					
Test for overall effect: Z = 3.43 (P = 0.00060)					

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

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

Comparison: 2 Routine calcium supplementation in pregnancy by hypertension risk

Outcome: 2 Pre-eclampsia

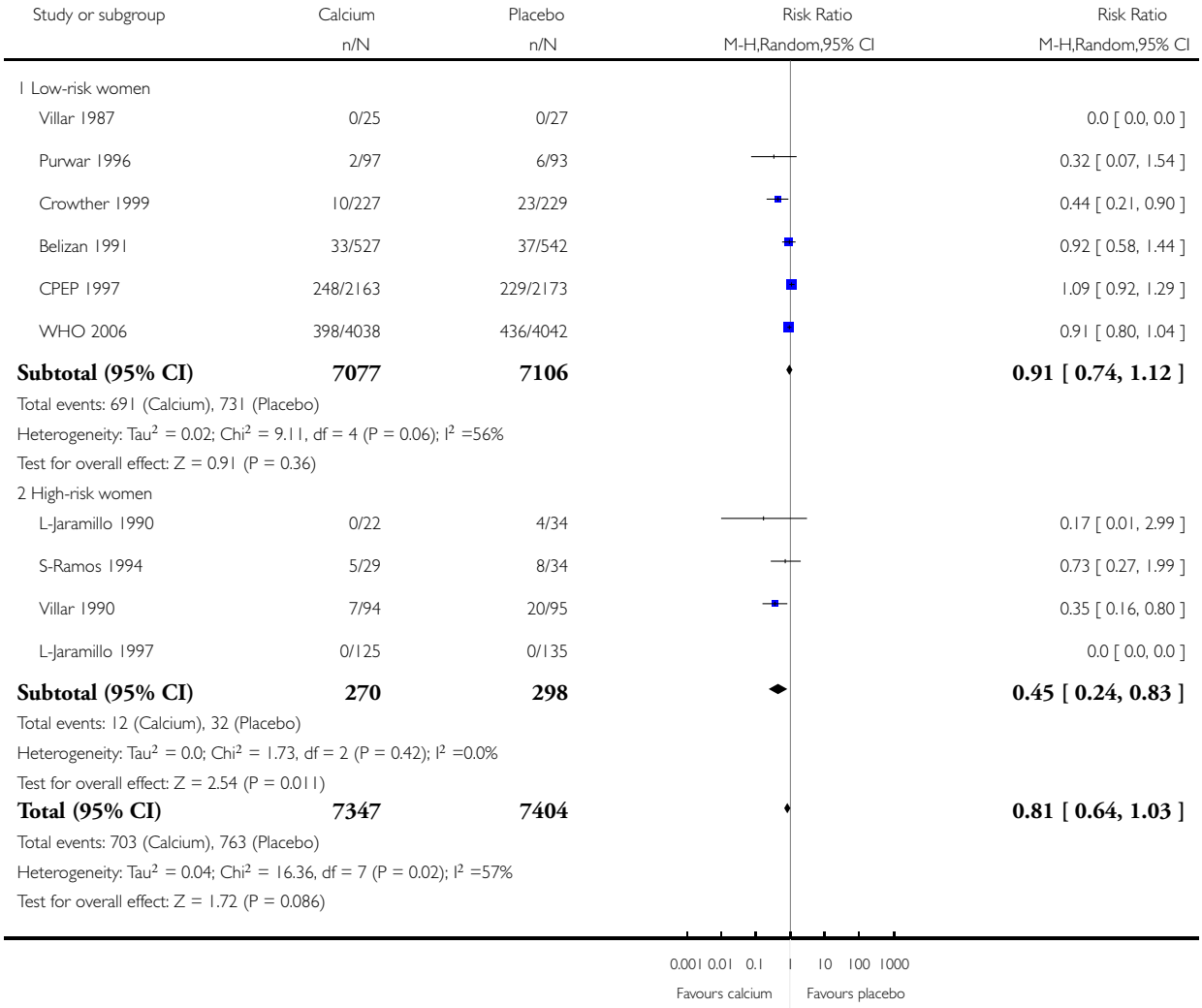


Analysis 2.13. Comparison 2 Routine calcium supplementation in pregnancy by hypertension risk, Outcome 13 Preterm birth.

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

Comparison: 2 Routine calcium supplementation in pregnancy by hypertension risk

Outcome: 13 Preterm birth

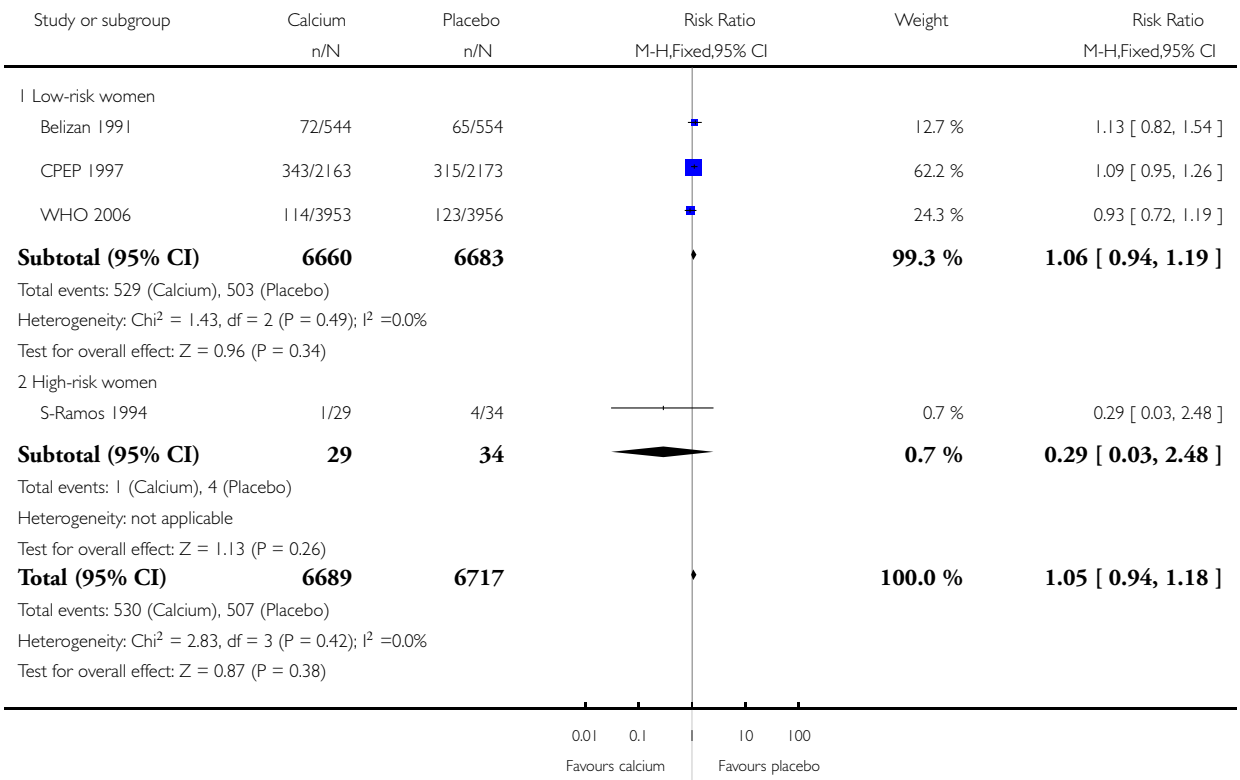


Analysis 2.16. Comparison 2 Routine calcium supplementation in pregnancy by hypertension risk, Outcome 16 Admission to neonatal intensive care unit.

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

Comparison: 2 Routine calcium supplementation in pregnancy by hypertension risk

Outcome: 16 Admission to neonatal intensive care unit



Analysis 2.18. Comparison 2 Routine calcium supplementation in pregnancy by hypertension risk, Outcome 18 Stillbirth or death before discharge from hospital.

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

Comparison: 2 Routine calcium supplementation in pregnancy by hypertension risk

Outcome: 18 Stillbirth or death before discharge from hospital

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low-risk women				
Villar 1987	0/25	0/27		0.0 [0.0, 0.0]
L-Jaramillo 1989	0/49	0/43		0.0 [0.0, 0.0]
Purwar 1996	0/97	0/93		0.0 [0.0, 0.0]
Crowther 1999	2/227	1/229		2.02 [0.18, 22.09]
Belizan 1991	6/558	7/567		0.87 [0.29, 2.58]
CPEP 1997	27/2163	25/2173		1.08 [0.63, 1.86]
WHO 2006	142/4181	166/4197		0.86 [0.69, 1.07]
Subtotal (95% CI)	**7300**	**7329**		**0.89 [0.73, 1.09]**
Total events: 177 (Calcium), 199 (Placebo)				
Heterogeneity: Chi^2 = 1.07, df = 3 (P = 0.78); I^2 =0.0%				
Test for overall effect: Z = 1.11 (P = 0.27)				
2 High-risk women				
S-Ramos 1994	0/29	1/34		0.39 [0.02, 9.20]
Villar 1990	0/94	0/95		0.0 [0.0, 0.0]
L-Jaramillo 1997	0/125	0/135		0.0 [0.0, 0.0]
Subtotal (95% CI)	**248**	**264**		**0.39 [0.02, 9.20]**
Total events: 0 (Calcium), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.59 (P = 0.56)				
Total (95% CI)	**7548**	**7593**		**0.89 [0.73, 1.09]**
Total events: 177 (Calcium), 200 (Placebo)				
Heterogeneity: Chi^2 = 1.33, df = 4 (P = 0.86); I^2 =0.0%				
Test for overall effect: Z = 1.15 (P = 0.25)				

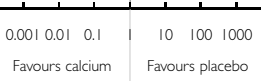
Analysis 3.1. Comparison 3 Routine calcium supplementation in pregnancy by study sample size, Outcome 1 High blood pressure (with or without proteinuria).

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

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

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

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Studies with < 400 participants					
Villar 1987	1/25	3/27		0.8 %	0.36 [0.04, 3.24]
L-Jaramillo 1990	3/22	24/34		3.1 %	0.19 [0.07, 0.57]
S-Ramos 1994	9/29	22/34		7.7 %	0.48 [0.26, 0.87]
L-Jaramillo 1989	2/55	12/51		1.8 %	0.15 [0.04, 0.66]
Villar 1990	3/90	8/88		2.2 %	0.37 [0.10, 1.34]
Purwar 1996	8/97	27/93		5.7 %	0.28 [0.14, 0.59]
Niromanesh 2001	10/15	11/15		10.2 %	0.91 [0.57, 1.45]
Subtotal (95% CI)	**333**	**342**		**31.5 %**	**0.38 [0.21, 0.68]**
Total events: 36 (Calcium), 107 (Placebo)					
Heterogeneity: Tau^2 = 0.38; Chi^2 = 18.26, df = 6 (P = 0.01); I^2 =67%					
Test for overall effect: Z = 3.20 (P = 0.0014)					
2 Studies with =/> 400 participants					
Crowther 1999	34/227	38/229		11.4 %	0.90 [0.59, 1.38]
Belizan 1991	57/579	87/588		14.6 %	0.67 [0.49, 0.91]
CPEP 1997	509/2163	565/2173		21.2 %	0.91 [0.82, 1.00]
WHO 2006	613/4151	645/4161		21.3 %	0.95 [0.86, 1.05]
Subtotal (95% CI)	**7120**	**7151**		**68.5 %**	**0.90 [0.81, 1.00]**
Total events: 1213 (Calcium), 1335 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.61, df = 3 (P = 0.20); I^2 =35%					
Test for overall effect: Z = 2.04 (P = 0.041)					
Total (95% CI)	**7453**	**7493**		**100.0 %**	**0.70 [0.57, 0.86]**
Total events: 1249 (Calcium), 1442 (Placebo)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 34.43, df = 10 (P = 0.00016); I^2 =71%					
Test for overall effect: Z = 3.43 (P = 0.00060)					



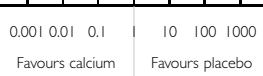
Analysis 3.2. Comparison 3 Routine calcium supplementation in pregnancy by study sample size, Outcome 2 Pre-eclampsia.

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

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

Outcome: 2 Pre-eclampsia

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Studies with < 400 participants					
Niromanesh 2001	1/15	7/15		3.1 %	0.14 [0.02, 1.02]
L-Jaramillo 1990	0/22	8/34		1.6 %	0.09 [0.01, 1.48]
Villar 1987	1/25	3/27		2.5 %	0.36 [0.04, 3.24]
S-Ramos 1994	4/29	15/34		8.6 %	0.31 [0.12, 0.84]
L-Jaramillo 1989	2/55	12/51		5.1 %	0.15 [0.04, 0.66]
Villar 1990	0/90	3/88		1.5 %	0.14 [0.01, 2.67]
Purwar 1996	2/97	11/93		4.9 %	0.17 [0.04, 0.77]
L-Jaramillo 1997	4/125	21/135		8.0 %	0.21 [0.07, 0.58]
Subtotal (95% CI)	**458**	**477**		**35.3 %**	**0.21 [0.12, 0.36]**
Total events: 14 (Calcium), 80 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.72, df = 7 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 5.78 (P < 0.00001)					
2 Studies with =/> 400 participants					
Crowther 1999	10/227	23/229		11.9 %	0.44 [0.21, 0.90]
Belizan 1991	15/579	23/588		13.1 %	0.66 [0.35, 1.26]
CPEP 1997	158/2163	168/2173		19.9 %	0.94 [0.77, 1.16]
WHO 2006	171/4151	186/4161		19.9 %	0.92 [0.75, 1.13]
Subtotal (95% CI)	**7120**	**7151**		**64.7 %**	**0.85 [0.69, 1.05]**
Total events: 354 (Calcium), 400 (Placebo)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.96, df = 3 (P = 0.17); I^2 =40%					
Test for overall effect: Z = 1.48 (P = 0.14)					
Total (95% CI)	**7578**	**7628**		**100.0 %**	**0.48 [0.33, 0.69]**
Total events: 368 (Calcium), 480 (Placebo)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 33.90, df = 11 (P = 0.00038); I^2 =68%					
Test for overall effect: Z = 3.88 (P = 0.00010)					



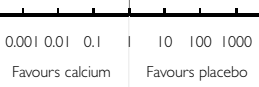
Analysis 3.13. Comparison 3 Routine calcium supplementation in pregnancy by study sample size, Outcome 13 Preterm birth.

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

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

Outcome: 13 Preterm birth

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Studies with < 400 participants				
Villar 1987	0/25	0/27		0.0 [0.0, 0.0]
L-Jaramillo 1990	0/22	4/34		0.17 [0.01, 2.99]
S-Ramos 1994	5/29	8/34		0.73 [0.27, 1.99]
Purwar 1996	2/97	6/93		0.32 [0.07, 1.54]
Villar 1990	7/94	20/95		0.35 [0.16, 0.80]
L-Jaramillo 1997	0/125	0/135		0.0 [0.0, 0.0]
Subtotal (95% CI)	**392**	**418**		**0.43 [0.24, 0.76]**
Total events: 14 (Calcium), 38 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.89, df = 3 (P = 0.60); I^2 =0.0%				
Test for overall effect: Z = 2.88 (P = 0.0040)				
2 Studies with =/> 400 participants				
Crowther 1999	10/227	23/229		0.44 [0.21, 0.90]
Belizan 1991	33/527	37/542		0.92 [0.58, 1.44]
CPEP 1997	248/2163	229/2173		1.09 [0.92, 1.29]
WHO 2006	398/4038	436/4042		0.91 [0.80, 1.04]
Subtotal (95% CI)	**6955**	**6986**		**0.93 [0.76, 1.13]**
Total events: 689 (Calcium), 725 (Placebo)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.25, df = 3 (P = 0.06); I^2 =59%				
Test for overall effect: Z = 0.72 (P = 0.47)				
Total (95% CI)	**7347**	**7404**		**0.81 [0.64, 1.03]**
Total events: 703 (Calcium), 763 (Placebo)				
Heterogeneity: Tau^2 = 0.04; Chi^2 = 16.36, df = 7 (P = 0.02); I^2 =57%				
Test for overall effect: Z = 1.72 (P = 0.086)				

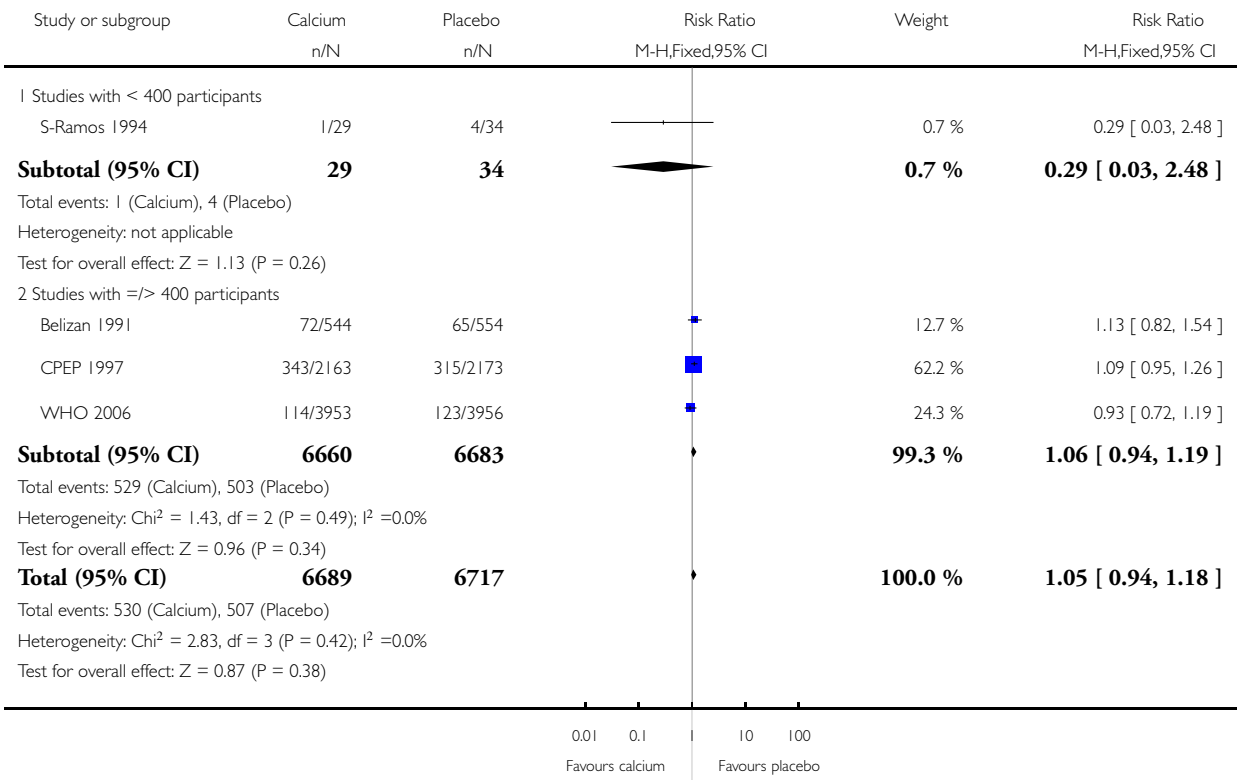


Analysis 3.16. Comparison 3 Routine calcium supplementation in pregnancy by study sample size, Outcome 16 Admission to neonatal intensive care unit.

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

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

Outcome: 16 Admission to neonatal intensive care unit



Analysis 3.18. Comparison 3 Routine calcium supplementation in pregnancy by study sample size, Outcome 18 Stillbirth or death before discharge from hospital.

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

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

Outcome: 18 Stillbirth or death before discharge from hospital

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Studies with < 400 participants				
Villar 1987	0/25	0/27		0.0 [0.0, 0.0]
S-Ramos 1994	0/29	1/34		0.39 [0.02, 9.20]
L-Jaramillo 1989	0/49	0/43		0.0 [0.0, 0.0]
Villar 1990	0/94	0/95		0.0 [0.0, 0.0]
Purwar 1996	0/97	0/93		0.0 [0.0, 0.0]
L-Jaramillo 1997	0/125	0/135		0.0 [0.0, 0.0]
Subtotal (95% CI)	**419**	**427**		**0.39 [0.02, 9.20]**
Total events: 0 (Calcium), 1 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.59 (P = 0.56)				
2 Studies with =/> 400 participants				
Crowther 1999	2/227	1/229		2.02 [0.18, 22.09]
Belizan 1991	6/558	7/567		0.87 [0.29, 2.58]
CPEP 1997	27/2163	25/2173		1.08 [0.63, 1.86]
WHO 2006	142/4181	166/4197		0.86 [0.69, 1.07]
Subtotal (95% CI)	**7129**	**7166**		**0.89 [0.73, 1.09]**
Total events: 177 (Calcium), 199 (Placebo)				
Heterogeneity: Chi² = 1.07, df = 3 (P = 0.78); I² =0.0%				
Test for overall effect: Z = 1.11 (P = 0.27)				
Total (95% CI)	**7548**	**7593**		**0.89 [0.73, 1.09]**
Total events: 177 (Calcium), 200 (Placebo)				
Heterogeneity: Chi² = 1.33, df = 4 (P = 0.86); I² =0.0%				
Test for overall effect: Z = 1.15 (P = 0.25)				

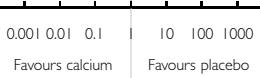
Analysis 4.2. Comparison 4 Routine calcium supplementation in pregnancy by baseline dietary calcium and study sample size, Outcome 2 Pre-eclampsia.

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

Comparison: 4 Routine calcium supplementation in pregnancy by baseline dietary calcium and study sample size

Outcome: 2 Pre-eclampsia

Study or subgroup	Calcium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate calcium/small study					
Villar 1987	1/25	3/27		2.5 %	0.36 [0.04, 3.24]
Villar 1990	0/90	3/88		1.5 %	0.14 [0.01, 2.67]
Subtotal (95% CI)	**115**	**115**		**4.0 %**	**0.26 [0.04, 1.50]**
Total events: 1 (Calcium), 6 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.51 (P = 0.13)					
2 Adequate calcium/large study					
Crowther 1999	10/227	23/229		11.9 %	0.44 [0.21, 0.90]
CPEP 1997	158/2163	168/2173		19.9 %	0.94 [0.77, 1.16]
Subtotal (95% CI)	**2390**	**2402**		**31.7 %**	**0.70 [0.33, 1.46]**
Total events: 168 (Calcium), 191 (Placebo)					
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 4.04$, df = 1 (P = 0.04); $I^2 = 75\%$					
Test for overall effect: Z = 0.96 (P = 0.34)					
3 Low calcium/small study					
L-Jaramillo 1990	0/22	8/34		1.6 %	0.09 [0.01, 1.48]
S-Ramos 1994	4/29	15/34		8.6 %	0.31 [0.12, 0.84]
L-Jaramillo 1989	2/55	12/51		5.1 %	0.15 [0.04, 0.66]
Purwar 1996	2/97	11/93		4.9 %	0.17 [0.04, 0.77]
L-Jaramillo 1997	4/125	21/135		8.0 %	0.21 [0.07, 0.58]
Subtotal (95% CI)	**328**	**347**		**28.2 %**	**0.21 [0.12, 0.38]**
Total events: 12 (Calcium), 67 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.26$, df = 4 (P = 0.87); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.25 (P < 0.00001)					
4 Low calcium/large study					
Belizan 1991	15/579	23/588		13.1 %	0.66 [0.35, 1.26]
WHO 2006	171/4151	186/4161		19.9 %	0.92 [0.75, 1.13]
Subtotal (95% CI)	**4730**	**4749**		**33.0 %**	**0.89 [0.74, 1.09]**
Total events: 186 (Calcium), 209 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.93$, df = 1 (P = 0.34); $I^2 = 0.0\%$					



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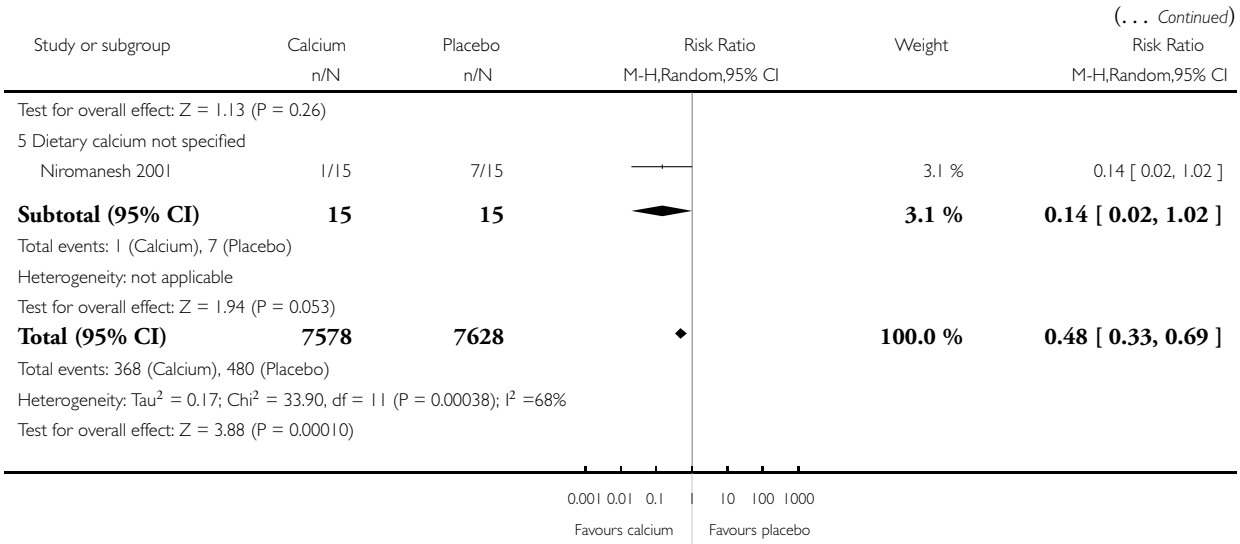

WHAT'S NEW

Last assessed as up-to-date: 1 March 2006.

1 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 3, 1998

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

CONTRIBUTIONS OF AUTHORS

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

Alvaro Atallah and Justus Hofmeyr prepared the protocol for the current Cochrane review.

Justus Hofmeyr prepared the data analysis and is primarily responsible for maintaining the review, with input from Lelia Duley and Alvaro Atallah.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

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

External sources

- UNDP/UNFPA/WHO/World Bank (HRP), Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy