Cochrane
Library

Cochrane Database of Systematic Reviews

Calcium and phosphorus supplementation of human milk for preterm infants (Review)

Harding JE, Wilson J, Brown J

Harding JE, Wilson J, Brown J.
Calcium and phosphorus supplementation of human milk for preterm infants.
Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD003310.
DOI: [10.1002/14651858.CD003310.pub2](https://doi.org/10.1002/14651858.CD003310.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	9
Figure 2.	10
Figure 3.	11
DISCUSSION	12
AUTHORS' CONCLUSIONS	13
ACKNOWLEDGEMENTS	13
REFERENCES	14
CHARACTERISTICS OF STUDIES	15
DATA AND ANALYSES	18
Analysis 1.1. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 1 Weight (g).	19
Analysis 1.2. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 2 Length (cm).	19
Analysis 1.3. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 3 Head circumference (cm).	20
Analysis 1.4. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 4 Serum alkaline phosphatase.	21
Analysis 1.5. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 5 Osteopenia.	21
APPENDICES	21
WHAT'S NEW	22
HISTORY	22
CONTRIBUTIONS OF AUTHORS	22
DECLARATIONS OF INTEREST	22
SOURCES OF SUPPORT	22
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	23
INDEX TERMS	23

[Intervention Review]

Calcium and phosphorus supplementation of human milk for preterm infants

Jane E Harding¹, Jess Wilson¹, Julie Brown¹¹Liggins Institute, The University of Auckland, Auckland, New Zealand**Contact address:** Jane E Harding, Liggins Institute, The University of Auckland, Auckland, 1001, New Zealand.
j.harding@auckland.ac.nz.**Editorial group:** Cochrane Neonatal Group.**Publication status and date:** New search for studies and content updated (conclusions changed), published in Issue 2, 2017.**Citation:** Harding JE, Wilson J, Brown J. Calcium and phosphorus supplementation of human milk for preterm infants. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD003310. DOI: [10.1002/14651858.CD003310.pub2](https://doi.org/10.1002/14651858.CD003310.pub2).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Preterm infants are born with low skeletal stores of calcium and phosphorus. Preterm human milk provides insufficient calcium and phosphorus to meet the estimated needs of preterm infants for adequate growth. Supplementation of human milk with calcium and phosphorus may improve growth and development of preterm infants.

Objectives

To determine whether addition of calcium and phosphorus supplements to human milk leads to improved growth and bone metabolism of preterm infants without significant adverse effects.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3), MEDLINE via PubMed (1966 to 14 April 2016), Embase (1980 to 14 April 2016) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 14 April 2016). We also searched clinical trials databases (11 May 2016) and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised and quasi-randomised trials comparing supplementation of human milk with calcium and/or phosphorus versus no supplementation in hospitalised preterm infants were eligible for inclusion in this review.

Data collection and analysis

Two review authors (JB, JW) independently extracted data and assessed trial quality using standard methods of the Cochrane Neonatal Review Group. We reported dichotomous data as risk ratios (RRs) and continuous data as mean differences (MDs) with 95% confidence intervals (CIs). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.

Main results

This is an update of a 2001 review that identified no eligible trials. One trial including 40 infants met the inclusion criteria for this review. Using GRADE criteria, we judged the quality of the evidence as low owing to risk of bias (inadequate reporting of methods of randomisation, allocation concealment and/or blinding) and imprecision (wide confidence intervals and data from a single small trial). We found no evidence of a difference between calcium and phosphorus supplementation versus no supplementation for neonatal growth outcomes (weight, length, head circumference) at any time point reported (two, four or six weeks postnatal age). At six weeks postnatal

age, supplementation with calcium/phosphorus was associated with a decrease in serum alkaline phosphatase concentration (MD -56.85 IU/L, 95% CI -101.27 to -12.43; one randomised controlled trial (RCT); n = 40 infants). Investigators provided no data on growth at 12 to 18 months, neonatal fractures, feed intolerance, breastfeeding or any of the prespecified childhood outcomes for this review (fractures, growth, neurodevelopmental outcomes).

Authors' conclusions

We identified one small trial including only 40 infants that compared supplementation of human milk with calcium and phosphorus versus no supplementation in hospitalised preterm infants. We judged the evidence to be of low quality and found no evidence of differences between groups for clinically important outcomes including growth and fractures. Although serum alkaline phosphatase concentration was reduced in the group receiving supplementation at six weeks postnatal age, this difference is unlikely to be of clinical significance. We conclude that evidence is insufficient to determine whether benefit or harm ensues when human milk is supplemented with calcium and/or phosphorus for the hospitalised preterm infant. We see no advantage of conducting further trials of this intervention because with the advent of multi-component human milk fortifier, supplementation of human milk with calcium and/or phosphorus alone is no longer common practice. Future trials should consider assessing effects of multi-component fortifiers with different mineral compositions on clinically important outcomes during the neonatal period and in later childhood.

PLAIN LANGUAGE SUMMARY

Does supplementation of human milk with calcium and phosphorus improve growth and development in preterm infants?

What is the issue?

When babies are born too early (preterm), they have very low stores of the minerals calcium and phosphorus needed for healthy bones and growth. Human milk may not contain sufficient minerals for these babies.

Why is this important?

Calcium and phosphorus are essential for healthy bones and normal growth and development. When a baby is born preterm and does not receive enough calcium and phosphorus, bone fractures and poor growth can occur.

What evidence did we find?

We searched for evidence in April 2016 and identified one randomised controlled trial including 40 babies. Investigators reported a small decrease in the concentration of alkaline phosphatase (an enzyme involved in bone growth) among infants who had received calcium/phosphorus supplementation. We found no difference in growth between infants who had been given human milk supplemented with extra calcium and phosphorus and infants who had received no supplementation. One small trial provided the evidence, and we judged the evidence to be of low quality. Researchers reported no follow-up of these babies into childhood.

What does this mean?

Evidence is insufficient to allow a judgement as to whether extra calcium and/or phosphorus provided to preterm babies confers benefit for their bones and growth. It is no longer very common to give calcium and phosphorus supplements alone, as human milk fortifiers now available include many other components as well as minerals to support the growth and development of preterm babies. We therefore suggest that future trials conducted to examine effects of mineral supplements in preterm babies include them in multi-component human milk fortifiers and assess clinically important outcomes into childhood.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Calcium supplementation compared with no calcium supplementation for preterm infants

Calcium supplementation compared with no calcium supplementation for preterm infants

Patient or population: preterm hospitalised infants

Setting: hospital setting

Intervention: calcium and/or phosphorus supplementation

Comparison: no supplement

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no calcium/phosphorus supplementation	Risk with calcium/phosphorus supplementation				
Weight (g) - weight at 6 weeks	Mean weight (g) - weight at 6 weeks was 2483 g	MD 138.5 g higher (82.16 lower to 359.16 higher)	-	40 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	
Length (cm) - length at 6 weeks	Mean length (cm) - length at 6 weeks was 47.04 cm	MD 0.77 cm higher (0.93 lower to 2.47 higher)	-	40 (1 RCT)	⊕⊕⊕⊖ Low ^{a,c}	
Head circumference (cm) - head circumference at 6 weeks	Mean head circumference (cm) - head circumference at 6 weeks was 34.31 cm	MD 0.33 cm higher (0.3 lower to 0.96 higher)	-	40 (1 RCT)	⊕⊕⊕⊖ Low ^{a,c}	
Bone fracture (neonatal) - not measured	-	-	-	-	-	This was not a prespecified outcome; included study did not report this outcome
Growth (childhood/adulthood) - not measured	-	-	-	-	-	Included study provided no follow-up into childhood
Bone mineral density (infant/childhood/adulthood) - not measured	-	-	-	-	-	Included study provided no follow-up into childhood

Fracture (childhood/adulthood) - not measured	-	-	-	-	-	-	Included study provided no follow-up into childhood
---	---	---	---	---	---	---	---

***Risk in the intervention group** (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; OR: odds ratio; RR: risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to the estimate of effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aRisk of bias: insufficient evidence to judge methods of randomisation, allocation concealment or blinding of personnel - downgraded one level

^bImprecision: wide confidence intervals and data from a single small study - downgraded one level

^cImprecision: evidence from a single small study - downgraded one level

BACKGROUND

Description of the condition

Human milk is the recommended nutritional source for full-term infants during at least the first six months of postnatal life (http://www.who.int/nutrition/topics/exclusive_breastfeeding/en/). For this group, breast milk supplies adequate substrate to meet the infant's nutritional demands and provides the infant with other substances that may afford some physiological advantage (e.g. immunoglobulins, gastrointestinal hormones). Breastfeeding may also contribute to maternal-infant bonding.

Description of the intervention

Human milk is recommended for enteral feeding of all preterm infants ([American Academy of Pediatrics 2014](#)). However, human milk provides insufficient quantities of various nutrients, including calcium and phosphorus, to meet the estimated needs of these infants.

Two-thirds of fetal body mineral content is acquired during the third trimester of pregnancy ([Itani 1991](#)). Therefore, preterm infants are born with low skeletal stores of calcium and phosphorus and require very high quantities of these minerals if they are to attain adequate postnatal skeletal growth. These requirements may not be met by feeding human milk alone ([Bhatia 2007](#)). Observational studies have shown that preterm infants fed human milk alone may have hypophosphataemia ([Atkinson 1983](#)), radiological evidence of poor bone mineralisation ([Atkinson 1983](#); [Rowe 1979](#)) and elevated alkaline phosphatase activity ([Rowe 1984](#)), and all of this may be associated with fractures and lower than expected growth rates ([Bhatia 2007](#)). Furthermore, early bone mineral content may predict peak bone mineral density and therefore lifelong fracture risk ([Winsloe 2009](#)). On the other hand, calcium and phosphorus supplements can be associated with adverse effects such as hypercalcaemia, feed intolerance ([Bozzetti 2009](#)) and elevated calcium, all of which are associated with nephrocalcinosis and renal damage in preterm infants ([Schell-Feith 2010](#)). Concern about development of metabolic bone disease might lead parents and clinicians to give formula rather than persisting with expressing and giving breast milk when such a decision is considered. For this reason, provision of supplements might influence the likelihood of continued breastfeeding and hence developmental outcomes.

How the intervention might work

Supplementation of human milk with calcium and phosphorus may improve body mineral stores and maintain or improve bone metabolism while improving growth.

Why it is important to do this review

We conducted this review to establish whether supplementing human milk with calcium and phosphorus leads to improved bone metabolism and growth outcomes for preterm infants.

OBJECTIVES

To determine whether addition of calcium and phosphorus supplements to human milk leads to improved growth and bone metabolism of preterm infants without significant adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs, including cluster-randomised trials but not cross-over trials (inappropriate study design). We included both published and unpublished studies and studies published only as abstracts, if assessment of study quality was possible and if they fulfilled other criteria for inclusion.

Types of participants

Preterm infants (< 37 weeks gestational age) receiving care within a hospital setting.

Types of interventions

Randomised controlled trials comparing human milk supplemented with calcium and/or phosphorus versus unsupplemented human milk.

Types of outcome measures

Primary outcomes

- Growth to discharge (including weight and z score, length and z score, head circumference and z score)
- Growth at 12 to 18 months (including weight and z score, length and z score, head circumference and z score)
- Bone metabolism (including serum alkaline phosphatase (ALP), bone mineral content (BMC), timing defined by the trialist)

Secondary outcomes

Neonatal outcomes

- Incidence of fractures
- Adverse effects including significant hypercalcaemia (> 3 mmol/L), nephrocalcinosis, impaired renal function
- Feed intolerance
- Breastfeeding (any) at discharge

Childhood/adulthood outcomes

- Incidence of fracture
- Growth (weight, height, age determined by trialist)
- Neurodevelopmental outcomes (as defined by trialist)

Search methods for identification of studies

Electronic searches

We used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see [the Cochrane Neonatal Group search strategy for specialized register](#)).

We conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3) in the Cochrane Library; MEDLINE via PubMed (1966 to 14 April 2016); Embase (1980 to 14 April 2016); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 14 April 2016) using the following search terms: (calcium OR phosphorus) AND (human milk OR breast milk OR breastmilk OR milk), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for full

search strategies for each database). We applied no language restrictions.

We searched (11 May 2016) clinical trials registries for ongoing and recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictrp/search/en/; the ISRCTN Registry).

Searching other resources

We searched the reference lists of included trials to identify unpublished and ongoing research.

Data collection and analysis

Selection of studies

For the 2016 update of this review, two review authors (JB, JW) independently examined titles and abstracts identified through electronic and manual searches, retrieved full texts of potential trials for inclusion, examined full texts for eligibility and made decisions on study inclusion or exclusion. A third review author (JH) was available to resolve disagreements.

Data extraction and management

We developed and piloted a data extraction form before gathering data. When available, we extracted data including reference source, eligibility criteria, study methods, participant characteristics, intervention and control details and clinical outcomes. Two review authors independently extracted data (JB, JW) and resolved disagreements by discussion or by referral to a third review author (JH). One review author (JW) entered data into Cochrane statistical software ([Review Manager 2013](#)) and a second review author (JB) checked the entered data for accuracy.

Assessment of risk of bias in included studies

Two review authors (JB, JW) independently assessed risk of bias for each study by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We encountered no disagreements.

Random sequence generation (checking for possible selection bias)

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

We assessed the method as having:

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

Allocation concealment (checking for possible selection bias)

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

We assessed the method as having:

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

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

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

We assessed the method as having:

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

Blinding of outcome assessment (checking for possible detection bias)

For each included study, we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received.

We assessed methods used to blind outcome assessment as having low, high or unclear risk of bias.

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

For each included study, we described completeness of data including attrition and exclusions from analysis. We stated whether attrition and exclusions were reported as well as numbers included in the analysis at each stage (compared with total randomised participants), reasons for attrition or exclusion when reported and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported, we planned to re-include missing data in the analyses undertaken.

We assessed the method as having:

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

Other sources of bias

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

We assessed whether each study was free of other problems that could put it at risk of bias and assigned each study as follows.

- Low risk of other bias.
- High risk of other bias.
- Unclear risk of other bias.

Measures of treatment effect

We used the numbers of events in control and intervention groups of each study to calculate risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data. We calculated mean differences (MDs) between treatment groups when outcomes were measured in the same way for continuous data, reported with 95% CIs.

Unit of analysis issues

The unit of analysis was the infant.

Dealing with missing data

When possible, we carried out analyses on an intention-to-treat basis for all outcomes and analysed all participants in the treatment group to which they were randomised, regardless of the actual treatment received. We attempted to contact the original investigators to request missing data, when possible. When high levels of attrition were observed (> 20%), we had planned to conduct sensitivity analyses to assess the influence of attrition bias. However, with only one included trial, we were unable to assess the effect of attrition bias.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We had planned to do this by assessing statistical heterogeneity using the Chi² test and the I² statistic. We classified heterogeneity as none (< 25%), low (25% to 49%), moderate (50% to 74%) or high (> 75%). We were going to consider an I² measurement greater than 50% and a low P value (< 0.10) in the Chi² test for heterogeneity to indicate substantial heterogeneity (Higgins 2011). We planned that when we detected substantial heterogeneity, we would explore possible explanations by performing sensitivity/subgroup analyses. However, with only one included trial, we were unable to make an assessment of heterogeneity.

Assessment of reporting biases

Reporting biases arise when dissemination of research findings is influenced by the nature and direction of results. Some types of reporting bias including publication bias, multiple publication bias and language bias reduce the likelihood that all studies eligible for a review will be retrieved. We aimed to conduct a comprehensive search for eligible studies and looked for duplication of data. We planned to assess publication bias by visually inspecting a funnel plot, if we had identified enough studies (≥ 10 trials). However, with only one included trial, we were unable to assess publication bias.

Two review authors examined the methods of each study for prespecified outcomes. If all prespecified outcomes were reported in the results, we assigned the study low risk of bias. If any prespecified outcomes were not reported in the results, we considered the study to carry higher risk of bias. If review authors uncovered reporting bias that could, in their opinion, introduce serious bias, we had planned to conduct a sensitivity analysis to determine the effects of including and excluding these studies in the analysis.

Data synthesis

We evaluated studies for bias, as above, and planned to restrict meta-analysis if bias would be compounded. We had planned to use a fixed-effect meta-analysis to combine data when it was reasonable to assume that studies were estimating the same underlying treatment effects. If evidence of clinical heterogeneity was sufficient to suggest that underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity, we had planned to undertake sensitivity and subgroup analyses to attempt to explain the heterogeneity. However, with only one included trial, we were unable to perform any meta-analyses.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

- Growth at discharge.
- Bone mineral density (neonatal).
- Fractures (neonatal).
- Growth (childhood).
- Bone mineral density (childhood).
- Fractures (childhood).

Two review authors (JB, JW) independently assessed the quality of the evidence for each outcome above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based on the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the *GradePro GDT* Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence based on four grades.

- High: We are very confident that the true effect lies close to the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

We summarised data from selected outcomes in [Summary of findings for the main comparison](#).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to assess effects of calcium supplementation alone, phosphorus supplementation alone and combined supplementation with calcium and phosphorus. Trials were insufficient for subgroup analyses.

Sensitivity analysis

For this 2016 update, we were unable to conduct sensitivity analysis owing to lack of evidence.

RESULTS

Description of studies

Results of the search

For the 2001 review, review authors identified no included studies, excluded 11 studies ([Characteristics of excluded studies](#)) and found

one study that was awaiting assessment ([Characteristics of studies awaiting classification](#)). For this 2016 update, searches yielded 808 potential studies, and we excluded 804 of these. We assessed three studies (four publications) for eligibility. We included one trial (two publications) ([Torabi 2014](#)), excluded one ([Carroll 2011](#)) and classified one as awaiting assessment ([Characteristics of studies awaiting classification](#)). See [Figure 1](#).

Figure 1. Study flow diagram (2016).

Included studies

We included one trial (two publications) in this 2016 updated review ([Torabi 2014](#)).

- Participants: Investigators randomised 40 infants born before 37 weeks gestation with birth weight below 2.5 kg.
- Setting: The trial was conducted in Iran.
- Interventions and comparisons: Researchers compared breast milk supplemented with calcium, phosphorus and vitamin D versus breast milk and vitamin D only.
- Outcomes: Data showed growth to discharge, bone metabolism and osteopenia. Study authors provided no data on growth at 12 to 18 months, adverse effects, feed intolerance or breastfeeding

at discharge and no data on other prespecified childhood/adulthood outcomes of this review (bone metabolism, incidence of fractures).

Excluded studies

Review authors excluded 11 studies in 2001 ([Characteristics of excluded studies](#)). We excluded one study for the 2016 update, as both intervention and control groups received supplementation ([Carroll 2011](#)).

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#).

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

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Randomisation

[Torabi 2014](#) reported that participants were "randomly divided into two groups"; we judged this trial to have unclear risk of bias for randomisation.

Allocation concealment

We judged [Torabi 2014](#) to have unclear risk of bias for allocation concealment owing to lack of methodological details.

Blinding

Performance bias

We judged [Torabi 2014](#) to have unclear risk of performance bias owing to lack of methodological detail.

Detection bias

We judged [Torabi 2014](#) to have low risk of detection bias, as outcome assessors were blinded to treatment allocation.

Incomplete outcome data

We judged [Torabi 2014](#) to have low risk of attrition bias, as investigators identified no losses to follow-up.

Selective reporting

[Torabi 2014](#) reported all prespecified outcomes, and we judged the trial to have low risk of reporting bias.

Other potential sources of bias

We identified no other sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison Calcium supplementation compared with no calcium supplementation for preterm infants](#)

Calcium and phosphorus supplementation versus no supplementation

Primary outcomes

Growth to discharge

Weight (grams (g))

[Torabi 2014](#) found no evidence of a difference in weight between infants who received calcium and phosphorus supplementation and those given no supplementation at two weeks (MD 52.50 g, 95% CI -155.44 to 260.44; one RCT; n = 40 infants), four weeks (MD 60.00 g, 95% CI -151.39 to 271.39; one RCT; n = 40 infants) or six weeks (MD 138.50 g, 95% CI -82.16 to 359.16; one RCT; n = 40 infants) postnatal age. We judged the evidence to be of *low quality* and downgraded the quality for risk of bias (insufficient details to judge randomisation, allocation concealment or blinding of personnel) and imprecision (wide confidence intervals, single small trial).

Length (cm)

[Torabi 2014](#) found no evidence of a difference in length between infants who received calcium and phosphorus supplementation and those given no supplementation at two weeks (MD 0.34 cm, 95%CI -1.36 to 2.04; one RCT; n = 40 infants), four weeks (MD 0.47

cm; 95%CI -1.20 to 2.14; one RCT; n = 40 infants) or six weeks (MD 0.77 cm, 95% CI -0.93 to 2.47; one RCT; n = 40 infants). We judged the evidence to be of *low quality* and downgraded the quality for risk of bias (insufficient details to judge randomisation, allocation concealment or blinding of personnel) and imprecision (single small trial).

Head circumference (cm)

[Torabi 2014](#) found no evidence of a difference in head circumference between infants who received calcium and phosphorus supplementation and those given no supplementation at two weeks (MD 0.19 cm, 95%CI -0.42 to 0.80; one RCT; n = 40 infants), four weeks (MD 0.22 cm, 95%CI -0.39 to 0.83; one RCT; n = 40 infants) or six weeks (MD 0.33 cm, 95%CI -0.30 to 0.96; one RCT; n = 40 infants). We judged the evidence to be of *low quality* and downgraded the quality for risk of bias (insufficient details to judge randomisation, allocation concealment or blinding of personnel) and imprecision (single small trial).

Bone metabolism

Serum alkaline phosphatase (ALP) (IU/L)

[Torabi 2014](#) found no evidence of a difference in ALP between infants who received calcium and phosphorus supplementation and those given no supplementation at two weeks (MD -36.35 IU/L, 95% CI -91.14 to 18.44; one RCT; n = 40 infants) or four weeks (MD -34.90 IU/L, 95% CI -81.23 to 11.43; one RCT; n = 40 infants) but found that supplementation was associated with a decrease in serum ALP levels at six weeks postnatal age (MD -56.85 IU/L, 95% CI -101.27 to -12.43; one RCT; n = 40 infants).

Other outcomes of interest (not prespecified)

[Torabi 2014](#) reported osteopenia measured by wrist x-ray at six weeks postnatal age. Data showed no evidence of a difference between infants who received calcium and phosphorus supplementation and those given no supplementation (RR 0.62, 95% CI 0.33 to 1.15; one RCT; n = 40 infants).

Researchers provided no data on growth-related outcomes at 12 to 18 months.

Secondary outcomes

Neonatal outcomes

Researchers provided no data on incidence of fracture, adverse effects, feed intolerance or breastfeeding at discharge.

Childhood/adulthood outcomes

Incidence of fracture

Investigators provided no data for this outcome.

Neurodevelopmental outcomes

Investigators provided no data for these outcomes.

DISCUSSION

Summary of main results

For this updated review conducted in 2016, we included one trial of 40 infants that compared supplementation with calcium and phosphorus versus no supplementation in hospitalised preterm infants. We found no evidence of a difference between infants

supplemented with calcium and phosphorus and those given no supplementation for the primary outcomes of this review of growth and bone metabolism, except for a small decrease in alkaline phosphatase (ALP) concentrations at six weeks among infants who received calcium and phosphorus supplementation. Review authors considered this decrease unlikely to be of clinical significance. Evidence was based on the findings of a single small trial, which did not report long-term outcomes for childhood and adulthood ([Summary of findings for the main comparison](#)).

Overall completeness and applicability of evidence

High-quality evidence is insufficient to reveal whether supplementation with calcium and phosphorus improved growth and bone health of hospitalised preterm infants. In the single trial included in this review, infants were born relatively large (mean gestation 33 weeks) and therefore were at low risk of metabolic bone disease. These findings may not be applicable to smaller and more preterm infants at greater risk of bone disease who may be more likely to benefit from supplements, if such a benefit can occur. Supplementation with calcium and phosphorus alone is no longer common practice. The Cochrane systematic review on multi-component human milk fortification has provided evidence superseding the evidence provided in this review ([Brown 2016](#)).

Quality of the evidence

This updated review includes one trial of 40 infants. The evidence is limited by lack of methodological detail and imprecision. We were not able to make judgements about risk of bias. Evidence was based on data from a single small trial including wide confidence intervals associated with the summary treatment effect. Using GRADE criteria ([GradePro GDT](#)), we judged the evidence to be of *low quality*.

Potential biases in the review process

We have tried to minimise bias in the review process by having two independent review authors conduct data selection and extraction. We double-checked the data entered. We believe that we have conducted a systematic and thorough search of the literature using multiple electronic databases and clinical trials registries without restrictions on language, date of publication or status of publication (published or unpublished).

Agreements and disagreements with other studies or reviews

We identified no other studies or reviews reporting on comparison of calcium and phosphorus supplementation of human milk for preterm infants versus no fortification. Supplementation with calcium and phosphorus alone is no longer common practice, but calcium and phosphorus are commonly included in multi-component human milk fortifiers that are widely used. We refer the reader to the Cochrane review titled "Multi-nutrient fortification of human milk for preterm infants" ([Brown 2016](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Data on supplementation of human milk with calcium and phosphorus are insufficient to allow recommendations for practice.

Implications for research

Supplementation of human milk with minerals, usually as one component of a multi-component fortifier, has become common practice largely on the basis of metabolic studies conducted to evaluate the composition of human milk and the nutritional requirements of preterm infants. Small controlled studies have evaluated urinary excretion of minerals as a proxy for mineral accretion and therefore bone deposition and have provided no evidence of any short-term or long-term clinical benefit derived from mineral supplementation. Despite this, it is unlikely that new studies will evaluate supplementation of human milk with minerals alone versus no mineral supplementation. Assessment of the effect of supplementation of human milk with minerals may best be done in the context of manipulation of multi-component fortifier composition for very and extremely preterm infants at high risk of metabolic bone disease.

ACKNOWLEDGEMENTS

We would like to acknowledge the contributions of Carl Kuschel and Vazhkudai S Kumaran to the first version of this review in 2001 ([Kuschel 1998](#)).

REFERENCES

References to studies included in this review

Torabi 2014 {published data only}

* Torabi Z, Moemeni N, Ahmadiashar A, Mazloomzadeh S. The effect of calcium and phosphorus supplementation on metabolic bone disorders in premature infants. *JPMA. The Journal of the Pakistan Medical Association* 2014;**64**(6):635-9. [PUBMED: 25252480]

Torabi Z, Moemeni N, Mazloomzadeh S. Evaluation and comparison of calcium and phosphorus in the improvement of metabolic bone disorder in premature infants. *Archives of Disease in Childhood*. 2012; Vol. 97:A386. [DOI: [10.1136/archdischild-2012-302724.1354](https://doi.org/10.1136/archdischild-2012-302724.1354)]

References to studies excluded from this review

Atkinson 1989 {published and unpublished data}

Atkinson SA, Whyte RK, Fraser D, Stanhope R. A randomized trial of calcium and phosphorus supplements in low birthweight infants fed mother's milk. *Proceedings of the Canadian Federation of Biological Sciences* 1989;**32**:Abstract.

Carroll 2011 {published data only}

* Carroll WF, Fabres J, Nagy TR, Frazier M, Roane C, Pohlandt F, et al. Results of extremely-low-birth-weight infants randomized to receive extra enteral calcium supply. *Journal of Pediatric Gastroenterology and Nutrition* 2011;**53**(3):339-45.

Faerk 2000 {published data only}

Faerk J, Petersen S, Petersen B, Michaelsen KF. Diet and bone mineral content at term in premature infants. *Pediatric Research* 2000;**47**(1):148-56.

Greer 1988 {published and unpublished data}

Greer FR, McCormick A. Improved bone mineralization and growth in premature infants fed fortified own mother's milk. *Journal of Pediatrics* 1988;**112**(6):961-9.

Gross 1987 {published data only}

Gross SJ. Bone mineralization in preterm infants fed human milk with and without mineral supplementation. *Journal of Pediatrics* 1987;**111**(3):450-8.

Gupta (unpublished data) {unpublished data only}

Gupta G. Unpublished data.

Hall 1993 {published data only}

Hall RT, Wheeler RE, Rippetoe LE. Calcium and phosphorus supplementation after initial hospital discharge in breast-fed infants of less than 1800 grams birth weight. *Journal of Perinatology* 1993;**13**(4):272-8.

Lucas 1996 {published and unpublished data}

Lucas A, Fewtrell MS, Morley R, Lucas PJ, Baker BA, Lister G, et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. *American Journal of Clinical Nutrition* 1996;**64**(2):142-51.

Salle 1986 {published data only}

Salle B, Senterre J, Putet G, Rigo J. Effects of calcium and phosphorus supplementation on calcium retention and fat absorption in preterm infants fed pooled human milk. *Journal of Pediatric Gastroenterology and Nutrition* 1986;**5**(4):638-42.

Sann 1985 {published data only}

Sann L, Loras B, David L, Durr F, Simonnet C, Baltassat P, et al. Effect of phosphorus supplementation to breast fed very low birthweight infants on urinary calcium excretion, serum immunoreactive parathyroid hormone and plasma 1,25-dihydroxy-vitamin D concentration. *Acta Paediatrica Scandinavica* 1985;**74**(5):664-8.

Schanler 1988 {published data only}

Schanler RJ, Garza C. Improved mineral balance in very low birth weight infants fed fortified human milk. *Journal of Pediatrics* 1988;**112**(3):452-6.

Senterre 1983 {published data only}

Senterre J, Putet G, Salle B, Rigo J. Effects of vitamin D and phosphorus supplementation on calcium retention in preterm infants fed banked human milk. *Journal of Pediatrics* 1983;**103**(2):305-7.

References to studies awaiting assessment

Boehm 1988 {published data only}

* Boehm G, Kirchner B. Calcium and phosphorus homeostasis in very-low-birth-weight infants appropriate for gestational age fed human milk. *Biomedica Biochimica Acta* 1988;**47**(6):529-36.

Kamali 2014 {published data only}

Kamali K, Pishva N, Deireh E. The effects of low and high dose oral calcium and phosphorus supplementation on nephrocalcinosis diagnosed by sonography in premature and low birth weight neonates. *Iranian Journal of Medical Sciences* 2014;**39**(6):559-64. [PUBMED: 25429179]

Additional references

American Academy of Pediatrics 2014

American Academy of Pediatrics Committee on Nutrition. In: Kleinman RE, Greer FR editor(s). *Pediatric Nutrition Handbook*. Elk Grove Village, IL: American Academy of Pediatrics, 2014.

Atkinson 1983

Atkinson SA, Radde IC, Anderson GH. Macromineral balances in premature infants fed their own mothers' milk or formula. *Journal of Pediatrics* 1983;**102**(1):99-106.

Bhatia 2007

Bhatia J. Human milk and the premature infant. *Journal of Perinatology* 2007;**27**:s71-4.

Bozzetti 2009

Bozzetti V, Tagliabue P. Metabolic bone disease in preterm newborn: an update on nutritional issues. *Italian Journal of Pediatrics* 2009;**35**:20.

Brown 2016

Brown JVE, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: [10.1002/14651858.CD000343.pub3](https://doi.org/10.1002/14651858.CD000343.pub3)]

GradePro GDT [Computer program]

GRADEpro Guideline Development Tool [Software] [Computer program]. GRADEpro GDT. GRADEpro.org: McMaster University (developed by Evidence Prime, Inc.), 2015.

Guyatt 2011a

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [PUBMED: 21195583]

Guyatt 2011b

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407-15. [PUBMED: 21247734]

Guyatt 2011c

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283-93. [PUBMED: 21839614]

Guyatt 2011d

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294-302. [PUBMED: 21803546]

Guyatt 2011e

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence - indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303-10. [PUBMED: 21802903]

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Itani 1991

Itani O, Tsang RC. Calcium, phosphorus, and magnesium in the newborn: pathophysiology and management. In: Hay WW Jr

editor(s). *Neonatal Nutrition and Metabolism*. St. Louis: Mosby-Year Book, Inc., 1991:171-202.

Kuschel 1998

Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants (Cochrane Review). *Cochrane Database of Systematic Reviews* 1998, Issue Issue 4. [DOI: [10.1002/14651858.CD000343](https://doi.org/10.1002/14651858.CD000343)]

Review Manager 2013 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2013.

Rowe 1979

Rowe JC, Wood DH, Rowe DW, Raisz LG. Nutritional hypophosphatemic rickets in a premature infant fed breast milk. *New England Journal of Medicine* 1979;**300**(6):293-6.

Rowe 1984

Rowe J, Rowe D, Horak E, et al. Hypophosphatemia and hypercalciuria in small premature infants fed human milk: evidence for inadequate dietary phosphorus. *Journal of Pediatrics* 1984;**104**(1):112-7.

Schell-Feith 2010

Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. *Pediatric Nephrology* 2010;**25**:221.

Schünemann 2013

Schünemann H, Brozek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. www.guidelinedevelopment.org/handbook. Updated October 2013.

Winsloe 2009

Winsloe C, Earl S, Dennison EM, Cooper C, Harvey NC. Early life factors in the pathogenesis of osteoporosis. *Current Osteoporosis Reports* 2009;**7**(4):140-4.

References to other published versions of this review

Kuschel 2001

Kuschel CA, Harding JE, Kumaran VS. Calcium and phosphorus supplementation of human milk for preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: [10.1002/14651858.CD003310](https://doi.org/10.1002/14651858.CD003310)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Torabi 2014

Methods	Parallel randomised controlled trial
Participants	<p>Number of babies: 40</p> <p>Gestational age (mean (SD)): intervention: 33.3 (1.7); control: 33.3 (1.8)</p> <p>Inclusion criteria: gestational age < 37 weeks and birth weight < 2500 grams; medically stable and breastfed only</p> <p>Exclusion criteria: "Neonates with TPN and being nil per oral (NPO) for more than one week, receiving medications interfering with vitamin D metabolism (anticonvulsants, diuretics, corticosteroids etc.), those with sepsis syndrome, significant respiratory, neurologic, renal, genetic, cardiovascular, hepatic or gastrointestinal diseases as well as neonates whose mothers had osteomalacia, diabetes, parathyroid gland disease and renal disorders were excluded from the study" (Subjects and Methods, p.636)</p> <p>Setting: Valie-e-Asr Hospital of Zanjan City, in Iran</p> <p>Timing: December 2010-June 2011</p>
Interventions	<p>Intervention: calcium 45 mg/kg/d and phosphorus 24 mg/kg/d supplement (in addition to breast milk and vitamin D) (n = 20)</p> <p>vs</p> <p>Control: breast milk and Vitamin D only (n = 20)</p>
Outcomes	<p>Prespecified outcomes:</p> <ul style="list-style-type: none"> - Serum calcium, phosphorus and alkaline phosphatase levels - measured every 2 weeks - Growth parameters (weight, height, head circumference) - measured every 2 weeks - Osteopenia - assessed by wrist X-ray at end of study
Notes	<p>Funding: not stated</p> <p>Intention-to-treat analysis: yes</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly divided into two groups" (p.636)
Allocation concealment (selection bias)	Unclear risk	This was not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Clinician: "All neonates received supplements and/or vitamin D at the ages of 10 days to 6 weeks by mothers under the supervision of a qualified person who did not have any role in data analysis" (p.636)</p> <p>Although they did not have a role in data analysis, this does not mean that they were blinded</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Outcome assessor was not aware of the study</p> <p>"At the 6th week, an x-ray of left wrist + physical exam was done by an expert and a pediatrician without being informed about the research project" (p.636)</p>

Torabi 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	All outcomes specified were reported
Other bias	Low risk	Groups were similar at baseline

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

Study	Reason for exclusion
Atkinson 1989	Published in abstract form only, with no clinical results available (data lost)
Carroll 2011	Both intervention and control groups received supplementation
Faerk 2000	No randomisation to unsupplemented control group
Greer 1988	Supplementation with calcium, phosphate and protein. This study is included in the review on multi-component fortification (Brown 2016)
Gross 1987	Mineral supplementation was provided in the form of multi-component fortifier or premature formula. This study is included in the multi-component fortification review (Brown 2016)
Gupta (unpublished data)	Comparision of unsupplemented human milk vs human milk supplemented with calcium and with calcium and phosphorus. Concerns about the randomisation process and disparity between control and treatment groups
Hall 1993	Intervention performed on preterm infants at discharge from hospital
Lucas 1996	Supplementation of human milk with a multi-component fortifier vs supplementation with phosphate alone. This study is included in the review on multi-component fortification (Brown 2016)
Salle 1986	No prespecified clinical outcomes. All outcomes biochemical
Sann 1985	No prespecified clinical outcomes. Outcomes biochemical (urinary calcium and phosphate losses)
Schanler 1988	Not randomised
Senterre 1983	Not randomised

Characteristics of studies awaiting assessment *[ordered by study ID]*
Boehm 1988

Methods	Not known
Participants	Not known
Interventions	Not known

Boehm 1988 (Continued)

Outcomes	Not known
Notes	

Kamali 2014

Methods	"Randomized controlled trial"
Participants	37 preterm infants with birth weight < 1500 g or gestational age < 34 weeks
Interventions	Two different doses of calcium (75 vs 230 mg/kg/d) and phosphorus (50 vs 110 mg/kg/d) were prescribed; laboratory and sonographic data were then documented and evaluated
Outcomes	Nephrocalcinosis
Notes	Unclear if this study meets inclusion criteria for this review. Study authors are being contacted

DATA AND ANALYSES

Comparison 1. Calcium supplementation versus no calcium supplementation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight (g)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Weight at 2 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	52.5 [-155.44, 260.44]
1.2 Weight at 4 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	60.00 [-151.39, 271.39]
1.3 Weight at 6 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	138.5 [-82.16, 359.16]
2 Length (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Length at 2 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.34 [-1.36, 2.04]
2.2 Length at 4 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.47 [-1.20, 2.14]
2.3 Length at 6 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.77 [-0.93, 2.47]
3 Head circumference (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Head circumference at 2 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.42, 0.80]
3.2 Head circumference at 4 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.39, 0.83]
3.3 Head circumference at 6 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	0.33 [-0.30, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Serum alkaline phosphatase	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Serum ALP at 2 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-36.35 [-91.14, 18.44]
4.2 Serum ALP at 4 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-34.90 [-81.23, 11.43]
4.3 Serum ALP at 6 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-56.85 [-101.27, -12.43]
5 Osteopenia	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.33, 1.15]

Analysis 1.1. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 1 Weight (g).

Analysis 1.2. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 2 Length (cm).

Analysis 1.3. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 3 Head circumference (cm).

Analysis 1.4. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 4 Serum alkaline phosphatase.

Analysis 1.5. Comparison 1 Calcium supplementation versus no calcium supplementation, Outcome 5 Osteopenia.

APPENDICES

Appendix 1. Standard search methods

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomised controlled trial or controlled clinical trial or randomised or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Date	Event	Description
9 September 2016	New citation required and conclusions have changed	In 2016, we updated the review and included a new trial (Torabi 2014). Two trials are awaiting assessment
9 September 2016	New search has been performed	We updated the search and added 'Summary of findings' tables

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 4, 2001

Date	Event	Description
14 September 2008	Amended	We converted the review to new review format
21 June 2001	New citation required and conclusions have changed	We made substantive amendments to the review

CONTRIBUTIONS OF AUTHORS

Jane Harding was an author of the original version of this review. She contributed to the update, interpreted results and provided feedback on versions throughout the process.

Julie Brown was responsible for preparation of drafts of the updated review in 2016. She conducted study selection and data extraction and double-checked data entry.

Jess Wilson conducted study selection and data extraction and double-checked data entry.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- National Women's Hospital, Auckland, New Zealand.
- University of Auckland, Auckland, New Zealand.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been Federally funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C

- National Institute for Health Research, UK.

Editorial support for Cochrane Neonatal has been funded by a UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the review authors and are not necessarily those of the NHS, the NIHR or the UK Department of Health

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the text of this review to reflect new methods of reporting for Cochrane reviews and have included the GRADE assessment and [Summary of findings for the main comparison](#). We have expanded methodological aspects of the review as per standard Cochrane Neonatal Review Group procedure.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Milk, Human; Alkaline Phosphatase [blood]; Calcium [*administration & dosage]; Infant, Premature; Phosphorus [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn