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Calcium and vitamin D for increasing bone mineral density in premenopausal women (Protocol)

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[Intervention Protocol]

Calcium and vitamin D for increasing bone mineral density in premenopausal women

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of calcium and vitamin D supplementation singly or in combination for reducing fractures and increasing bone mineral density in healthy premenopausal women.

BACKGROUND

Description of the condition

Osteoporosis (OP) is characterized by low bone mineral density (BMD) and impaired quality of bone, and is considered a major public health concern worldwide. The main consequence of low BMD is fragility fractures, mainly at the hip, spine and wrist (NIH 1993). BMD in later life is a function of peak bone mass (the maximum bone mass attained in a person's life) and the rate of subsequent bone loss (Hansen 1991). Premenopausal bone mass is as important as bone loss in the postmenopausal period for prediction of fracture. Fragility fractures may lead to excess mortality, morbidity, low quality of life, and chronic pain (Borgström 2013; Papaioannou 2010).

It is estimated that OP affects about 200 million people worldwide, and 75 million of them are from developed countries (Europe, Japan and USA) (Kanis 2007). In the year 2000, 9 million new fragility fractures occurred, including 1.6 million on the hip, 1.7 million in the wrist and1.4 million on the spine (Johnell 2004). OP prevention is feasible and should be addressed throughout the life course, improving peak bone mass in childhood and early adult life and reducing age-related bone loss over adult life.

Description of the intervention

Dietary intake and supplementation therapy options for prevention and treatment of osteoporosis include Calcium and vitamin D. There are primarily obtained from two sources: food and supplements. Dairy products are a good source of dietary calcium. Regarding vitamin D, the main source in humans is the synthesis

in the skin through sun exposure, since vitamin D is only found in small quantities in certain foods. Calcium supplements are most commonly available as calcium citrate or calcium carbonate; vitamin D can be found as ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). A combination of both nutrients is available in different doses and presentations. Calcium and vitamin D supplements are also prescribed with anti-osteoporotic medications as they are thought to have additive effects. Clinical trials have been conducted in different age groups and populations, in order to assess the efficacy of this strategy.

There are Cochrane systematic reviews and meta-analyses of calcium and vitamin D supplementation for improving bone mineral density in children and postmenopausal women (Shea 2005; Winzenberg 2006; Winzenberg 2010). Currently, there is no known effect of calcium supplementation on femoral neck or lumbar spine BMD in children, but review authors found a small effect on total body bone mineral content (BMC) and upper limb BMD in this population (Winzenberg 2006). However, in their conclusion, the authors stated that the increase in BMD is unlikely to result in a clinically significant decrease in fracture risk (Winzenberg 2006). Another review showed that vitamin D supplementation had no effect on BMC, hip BMD and forearm BMD, but there was a trend to a small effect on lumbar spine BMD. The review concluded that these results do not support vitamin D supplementation to improve BMD in healthy children with normal vitamin D levels (Winzenberg 2010). Studies where the participants had low mean levels of vitamin D saw an effect of supplementation on BMD (Winzenberg 2010).

The review of calcium supplementation for postmenopausal women showed that calcium had a small effect on BMD when compared to placebo. Calcium reduced rates of bone loss after two or more years of treatment, but there was no effect seen on fracture risk (Shea 2005).

There remains some controversy in this field; Murad 2011 argues that a combination of both nutrients have a beneficial role in increasing bone density, muscle strength and a reduction of falls in the elderly. The United States Preventive Services Task Force (USPSTF), however, states that for primary prevention of fractures in postmenopausal women, there is some evidence of increased risk of cardiovascular damage that has led to disagreement about the balance of the benefits and harms of daily supplementation with more than 400 IU of vitamin D and more than 1000 mg of calcium (Moyer 2013).

In a systematic review (Malihi 2016) of the effect of long-term (> 24 weeks) vitamin D supplementation versus placebo, in both healthy and in different patient populations (adults aged over 18 years, men and women), the authors reported increased risks of hypercalcemias (RR = 1.54, 95% confidence interval (CI) 1.09 to 2.18, P = 0.01) and hypercalciuria (RR = 1.64, 95% CI 1.6 to 2.53, P = 0.03). However, in that review, the participants included a mix of different populations.

How the intervention might work

Calcium and vitamin D are simple and inexpensive interventions which potentially improve bone health. Calcium is needed for bone formation and is lost from the body (through urine and the renal system) each day, and needs to be replaced. Low serum calcium leads to increased parathyroid hormone (PTH) and increased bone loss. Therefore, maintaining adequate calcium intake is important. Vitamin D is essential for bone health, and its impact on bone health in adults is well accepted (IOM 2011). Vitamin D is integral to calcium homeostasis. It increases intestinal absorption of calcium. Bones are the main store of calcium in the body; as age increases intestinal absorption decreases.

In addition to the direct effects on bone, vitamin D has been associated with muscle strength and prevention of the risk of falls. As vitamin D receptors are found in different tissues, including muscle tissue, their activation leads to muscle protein synthesis. In this way, vitamin D supplements may improve muscle strength, and decrease the risk of falls (Bischoff-Ferrari 2009; Gupta 2010; Zhu 2010). Authors of a meta-analysis published in 2009 (Bischoff-Ferrari 2009) concluded that daily supplementation with more than 700 IU of vitamin D reduced the risk of falls in people over 65 years old (relative risk 0.81, 95% CI 0.71 to 0.92). This review had some heterogeneity in the studies included in the meta-analysis. However, in a meta-analysis performed by Murad, vitamin D supplementation had no effect on the risk of falls, regardless of dose and type of vitamin D used. Nevertheless, when vitamin D is co-administered with calcium, there is a reduction in the risk of falls in the elderly compared to placebo (odds ratio (OR) 0.83 95%CI 0.72 to 0.93). Heterogeneity was found across the studies despite using a random-effects model and subgroup analysis (Murad 2011).

Fracture risk is related to bone strength. Bone strength is contributed to by bone quantity (BMD) and bone quality. Bone quality takes into account structural and material properties, which cannot be assessed with BMD. Structural properties include geometry and microarchitecture; material properties are organization and composition of mineral and collagen components. It would be ideal to assess all the components of bone strength in order to have a better prediction of fracture risk. Nevertheless, BMD remains an important clinical measurement (Felsenberg 2005).

In addition, increased BMD in the context of other anti-osteoporotic treatments correlate with fracture risk reductions (Hochberg 1999) and BMD has been used as a surrogate outcome when assessing alternative dosage regimens for bisphosphonate (Rizzoli 2002; Winzenberg 2008). According to the Canadian Agency for Drugs and Technologies in Health (CADTH) report, BMD assessed by dual energy X-ray absorptiometry (DXA) predicts fragility fracture risk with a power of the diagnostic test (expressed as area under the curve (AUC)) from 0.60 to 0.95. An AUC close to 1.0 means a perfect test (Dunfield 2007).

DXA will be the ideal method of measuring BMD and BMC in relevant studies, as it is the reference standard measure that is used

to define osteoporosis (Lewiecki 2016).

Why it is important to do this review

The effect of calcium and vitamin D on BMD and fractures has been studied in children and in postmenopausal women, but less is known about the effects of calcium and vitamin D in premenopausal women. In February 2013, the USPSTF published a systematic review and meta-analysis of the use of calcium and vitamin D supplements to prevent fractures in adults. The USPSTF stated that the evidence at that time was insufficient to assess the benefits and harms for prevention of fractures in premenopausal women (Moyer 2013). Osteoporotic fractures are unlikely in this age group (premenopausal women) so other clinical variables should be measured, such as BMD and BMC. Existing systematic reviews have not accounted for more recent studies (Moyer 2013), and others in process are not yet finished (USPSTF 2016). Other Cochrane reviews in this topic area have focused in other populations such children or postmenopausal women (Shea 2005; Winzenberg 2006; Winzenberg 2010).

An up-to-date review in this area is important because premenopause is a period where peak bone mass can be potentially maintained or even improved to prevent fragility fractures in the future (Shea 2005). Given that calcium and vitamin D are two important modifiable factors to potentially improve bone density, it is important to determine the benefits and harms of the different doses/combination to maintain or improve BMD and bone quality in premenopausal women.

This review will be conducted according to the guidelines recommended by Cochrane Musculoskeletal (Ghogomu 2014).

OBJECTIVES

To assess the benefits and harms of calcium and vitamin D supplementation singly or in combination for reducing fractures and increasing bone mineral density in healthy premenopausal women.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs). Studies may be reported as full-text or published as abstract only. There will be no language restriction.

Types of participants

We will include trials in healthy premenopausal women aged 18 to 45 (and studies when the menopausal status is not specified but the age is reported), with or without vitamin D deficiency or calcium. Healthy women are defined as women with no known osteoporosis (OP) or osteopenia and without any chronic disease, cardiovascular condition, or autoimmune or inflammatory disease (e.g. rheumatoid arthritis, osteoarthritis, fibromyalgia, multiple sclerosis, systemic lupus erythematosus, diabetes mellitus and asthma).

We will exclude studies in pregnant and lactating women, in participants with coexisting medical conditions and with corticoid steroid-induced or other secondary causes of osteoporosis. When studies include also male participants, we will exclude them if information by sex cannot be extracted separately.

Types of interventions

We will include trials comparing calcium and vitamin D with placebo, focusing on three comparisons (regardless of type or dose of supplementation).

1. Calcium versus placebo.
2. Vitamin D versus placebo.
3. Calcium + vitamin D versus placebo.

We will conduct other subgroup analyses if needed (i.e. calcium plus vitamin D versus vitamin D alone, or calcium alone). We will exclude trials with a treatment period of less than three months.

We will exclude the following cointerventions of specific anti-osteoporosis therapy such as bisphosphonate, hormone replacement therapy, parathyroid hormone, selective estrogenic receptor modulators (SERMs), and strontium ranelate.

Types of outcome measures

Major outcomes

1. Total hip BMD.
2. Lumbar spine BMD.
3. Quality of life.
4. Vertebral fractures.
5. Non-vertebral fractures.
6. Withdrawals due to adverse events.
7. Serious adverse events (i.e., hospitalizations, or those resulting in disability or death).

Minor outcomes

1. We will collect data about all adverse events and all harm reported.

Search methods for identification of studies

Electronic searches

We will design a search strategy for the following databases.

- Cochrane Library via Wiley including CENTRAL, and Database of Reviews of Effects (DARE).
- MEDLINE via Ovid (1946 to present).
- Embase via Ovid (1947 to present).

The electronic search strategy for MEDLINE is outlined in Appendix 1. We will adapt this search strategy for use with other databases. We used the 'sensitivity and precision maximising version' filter designed to identify clinical trials described by Lefebvre 2009.

For assessments of adverse effects, we will search the web sites of the regulatory agencies US Food and Drug Administration-MedWatch (www.fda.gov/Safety/MedWatch/default.htm), European Medicines Evaluation Agency (www.emea.europa.eu), Australian Adverse Drug Reactions Bulletin (www.tga.gov.au/adr/aadrb.htm), and UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmacovigilance and drug safety updates (www.mhra.gov.uk).

We will also conduct a search of clinicaltrials.gov and the WHO trials portal (www.who.int/ictrp/en/).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

Unpublished results

We will search clinical trial registries for unpublished data. To obtain further information, we will contact the authors of studies on clinical registers or with results given only in graphic format or reported only as abstracts. If data are not available after contacting authors, the study will be described in the evidence table, but we will not include it in the meta-analysis.

Reference list scanning

We will search the reference lists of other reviews that are related in terms of the interventions and outcomes, and also search the reference lists of the included studies of this review.

Handsearching

We will handsearch conference abstract issues of key journals (Osteoporosis International, Journal of Bone and Mineral Research, Calcified Tissue International, Journal of Clinical Endocrinology and Metabolism, American Journal of Clinical Nutrition, European Journal of Clinical Nutrition, Journal of Nutrition, British Journal of Nutrition) for the past two years, to identify recent trials that have not yet been published in full.

We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (LM-S and PC) will independently screen titles and abstracts of all of the potentially relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (LM-S and PC) will screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (TW). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (prisma-statement.org/PRISMAStatement/Default.aspx) and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (LM-S) will extract study characteristics from included studies. A second review author (PC) will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location (country), study setting, withdrawals, and date of study.
2. Participants: sample size, mean age, age range, sex, ethnicity, baseline BMD, vitamin D status (if available), calcium and vitamin D intake (if available) and baseline data; inclusion criteria, and exclusion criteria.
3. Interventions: types of interventions (calcium alone, vitamin D alone or calcium plus vitamin D); comparison (versus placebo, or one of the interventions alone). If data are available we will report other alternative comparisons (i.e. calcium plus vitamin D versus vitamin D alone, or calcium alone). We will report dosage or type of vitamin D used (ergocalciferol or cholecalciferol), dosage and type of calcium supplement given, supplementation period and concomitant medications. We will exclude comparisons with other interventions, but we will report the type of comparisons found.

4. Outcomes: in all cases, we will extract both final and change from baseline values, but only the final value will be used. If data are analysed based on an intention-to-treat (ITT) or per-protocol (PP) sample, only the PP values will be used in the final analysis.
For dichotomous outcomes we will extract the number of events and number of participants per treatment group. For fractures and adverse events, we will extract data on both the number of events and the number of participants sustaining at least one event (for the analysis we will use the final value).
For continuous outcomes we will extract data as follows.

- Change in BMD: at the total hip and lumbar spine; we will extract means and standard deviations of the percentage of change and the number of participants per treatment group (for the analysis we will use the final change data per treatment group).
- Quality of life: we will extract means and standard deviations and number of participants in each treatment group in units expressed by the specific scale (we will use the final change data).

Only crude results will be extracted, not adjusted results.
If multiple time points are reported, the information on all time points will be extracted. We will analyse the effect by short-term supplementation (< 12 months) and long-term supplementation (≥ 12 months), for pooling in a meta-analysis.
When hip and vertebral data are available we will conduct analyses separately by intervention, population and dosage, type of vitamin D used (ergocalciferol or cholecalciferol) and type of calcium supplement given.
5. Characteristics of the design of the trial as outlined below in the Assessment of risk of bias in included studies section. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way and when data were transformed or estimated from a graph.
6. Notes: The trial funding and conflicts of interest of the trial will be described.
We will resolve disagreements by consensus or by involving a third person (PT). One review author (LM-S) will transfer data into the Review Manager (Review Manager 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.
We will use specific software (Plot Digitizer 2016) to extract data from graphs or figures. These data will also be extracted in duplicate.

Assessment of risk of bias in included studies

Two review authors (LM-S and PC) will independently assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreements will be resolved by discussion or by involving another author (PT). We will assess the risk of bias according to the following domains.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).

We will grade each potential source of bias as high, low or unclear risk, and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarize the 'Risk of bias' judgments across different studies for each of the domains listed. As well, we will consider the impact of missing data on key outcomes.
In the case of a lack of important study information, we will contact authors to obtain the information needed, using open-ended questions. Where the information on risk of bias comes from unpublished data or correspondence with trial lists, we will note this in the 'Risk of bias' table.
When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.
We will present the figures generated by the 'Risk of bias' tool to provide summary assessments of the risk of bias.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios or Peto odds ratios when the outcome is a rare event (approximately less than 10%), and use 95% confidence intervals (CIs). Continuous data will be analysed as mean difference (MD) or standardized mean difference (SMD), depending on whether the same scale is used to measure an outcome, and 95% CIs. We will enter data presented as a scale with a consistent direction of effect across studies.
When different scales are used to measure the same conceptual outcome (e.g. quality of life), SMDs will be calculated instead, with corresponding 95% CIs. SMDs will be back-translated to a typical scale (e.g. 0 to 10 for quality of life) by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of one instrument validated from the scale most used in the trials (Health Assessment Quality, SF-36, etc.)) as per chapter 12 of the*Cochrane Handbook* (Schünemann 2011)
In the 'Effects of interventions' results section and the 'Comments' column of the 'Summary of findings' table, we will provide the absolute per cent difference, the relative per cent change from baseline, and the number needed to treat for an additional beneficial (NNTB) or harmful (NNTH) outcome. The NNT will be provided only when the outcome shows a statistically significant difference.

For dichotomous outcomes, the NNTB will be calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator (Cates 2008). The NNTB for continuous measures will be calculated using the Wells calculator.

For dichotomous outcomes, the absolute risk difference will be calculated using the risk difference statistic in RevMan software (Review Manager 2014), and the result expressed as a percentage. The relative per cent change will be calculated as the risk ratio - 1 and expressed as a percentage.

For continuous outcomes, the absolute benefit will be calculated as the improvement in the intervention group minus the improvement in the control group, in the original units expressed as a percentage.

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. calcium versus placebo and vitamin D versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting. If the same comparisons (e.g. vitamin D versus different dosages of vitamin D) are combined in the same meta-analysis, we will separate by dose and comparison group. For the meta-analysis we will follow the procedures recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data when possible (e.g. when a study is identified as abstract only, when data are not available for all participants or the data are in a graphical analysis or adjusted). When this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis. Any assumptions and imputations to handle missing data will be clearly described and the effect of imputation will be explored by sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), the withdrawal rate will be calculated using the number of patients randomised in the group as the denominator.

For continuous outcomes (e.g. mean change in BMD), we will calculate the MD or SMD based on the number of patients analysed at that time point. If the number of patients analysed is not presented for each time point, the number of randomised patients in each group at baseline will be used.

Where feasible, we will compute missing standard deviations from other statistics such as standard errors, CIs or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). If standard deviations cannot be calculated, we will impute them (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

Clinical and methodological diversity will be assessed in terms of participants, interventions, outcomes and study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will be conducted by observing these data from the data extraction tables. Statistical heterogeneity will be assessed using the I^2 and Chi^2 statistical tests.

As recommended in the*Cochrane Handbook* (Deeks 2011), the interpretation of an I^2 value of 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity. As noted in the *Cochrane Handbook*, we will keep in mind that the importance of I^2 depends on: (i) magnitude and direction of effects; and (ii) strength of evidence for heterogeneity. The Chi^2 test will be interpreted where a P value ≤ 0.10 indicates evidence of statistical heterogeneity.

If we identify substantial heterogeneity we will report it and investigate possible causes by following the recommendations in section 9.6 of the *Cochrane Handbook* (Deeks 2011).

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small study biases. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry as outlined in section 10.4 of the *Cochrane Handbook* and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, and will follow the recommendations in section 10.4 of the *Handbook* (Sterne 2011).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organisation (apps.who.int/trialssearch) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

The primary analysis for our reviews for self-reported outcomes (e.g. quality of life) will be restricted to trials at low risk of detection and selection bias.

'Summary of findings' tables

We will create a 'Summary of findings' table using the following outcomes.

Major outcomes

1. Total hip BMD.
2. Lumbar spine BMD.
3. Quality of life.
4. Vertebral fractures.
5. Non-vertebral fractures.
6. Withdrawals due to adverse events.
7. Serious adverse events (i.e., hospitalizations, or those resulting in disability or death).

Minor outcomes

1. We will collect data about all adverse events and all harm reported.

Two people (LM-S and PC) will independently assess the quality of the evidence. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes, and report the quality of evidence as high, moderate, low, or very low. We will consider the following criteria for upgrading the quality of evidence, if appropriate: large effect, dose-response gradient, and plausible confounding effect. We will use methods and recommendations described in sections 8.5 and 8.7, and chapters 11 and 12, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Schünemann 2011). We will use GRADEpro software to prepare the 'Summary of findings' tables (GRADEpro GDT 2016). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary. We will provide the NNTB or NNTH, and absolute and relative per cent change in the Comments column of the 'Summary of findings' table, as described in the Measures of treatment effect section.

Subgroup analysis and investigation of heterogeneity

We will plan to carry out the following subgroup analyses for all major outcomes.

1. Dosage groups according to the results reported. We will follow the recommended dosages given by the Institute of Medicine (IOM 2011).

Vitamin D:

- ≤ 600 IU
- > 600 IU

Calcium:

- ≤ 1000mg
- > 1000 mg

2. Types of interventions
   - Calcium versus placebo
   - Vitamin D versus placebo
   - Calcium plus vitamin D versus placebo

3. Supplementation time
   - Short term < 12 months
   - Long term ≥ 12 months

4. Baseline vitamin D levels and baseline dietary calcium intake (if these are available), following the values established by the Institute of Medicine (IOM 2011).
   - Sufficiency > 30 ng/ml
   - Insufficiency 11 to 29 ng/ml
   - Deficiency <10 ng/ml

We will use the formal test for subgroup interactions in Review Manager (Review Manager 2014) and will use caution in the interpretation of subgroup analyses as advised in section 9.6 of the *Handbook* (Deeks 2011). The magnitude of the effects we will be compared between the subgroups by means of assessing the overlap of the confidence intervals (CIs) of the summary estimated. Non-overlap of the CIs indicates statistical significance.

Sensitivity analysis

We plan to carry out the following sensitivity analyses to investigate the robustness of the treatment effects.

1. We plan to carry out a sensitivity analysis to investigate the robustness of the treatment effects, by omitting trials where unpublished data and/or data imputed from figures or from other studies were used.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE(R) 1946 to present

Strategy:

1. exp vitamin d/
2. vitamin d.tw.
3. vitamin d2.tw.
4. vitamin d3.tw.
5. exp Ergocalciferols/
6. ergocalciferol$.tw.
7. exp Cholecalciferol/
8. cholecalciferol.tw.
9. hydroxycholecalciferol.tw.
10. calcitriol.tw.
11. dihydroxyvitamin D3.tw.
12. alphacalcidol.tw.
13. Calcium, Dietary/ or Calcium/
14. calcium.tw.
15. Calcium carbonate/
16. Calcium citrate/
17. or/1-16
18. exp Osteoporosis/
19. (bone adj3 loss).tw.
20. (bone adj3 mineral).tw.
21. bone mineral densit$.tw.
22. bmd.tw.
23. bmc.tw.
24. osteop$.tw.
25. Fractures, Bone/
26. exp Osteoporotic Fractures/
27. fractur$.tw.
28. or/18-27
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomized.ab.
32. placebo.ab.
33. clinical trials as topic.sh.
34. randomly.ab.
35. trial.ti.
36. or/29-35
37. exp animals/ not humans.sh.
38. 36 not 37

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- Conceiving, designing and coordinating the review: Lucia Méndez-Sánchez (LM-S), Patricia Clark (PC), Tania Winzenberg (TW), Peter Tugwell (PT).
- Designing protocol, search strategies and undertaking searches: LM-S, PC, TW, PT.
- Editor of English language in the protocol: TW.
- Screening search results and retrieved papers against inclusion criteria: LM-S, PC.
- Appraising quality of papers: LM-S, PC.
- Extracting data from papers: LM-S, PC, PT.
- Writing to authors of papers for additional information: LM-S, PC, PT.
- Data management for the review and entering data into RevMan: LM-S, PC, PT.
- Analysis and interpretation of data: LM-S, PC, TW, PT.
- Providing a research perspective: PC, TW, PT.
- Writing the review: LM-S, PC, TW, PT.
- Providing general advice on the review: LM-S, PC, TW, PT.
- Performing previous work that was the foundation of the current review: LM-S, PC, TW, PT.

DECLARATIONS OF INTEREST

The authors declare no conflict of interest.

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NOTES

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