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Calcium supplementation for weight reduction in overweight or obese people (Protocol)

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[Intervention Protocol]

Calcium supplementation for weight reduction in overweight or obese people

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of calcium supplementation for weight reduction in overweight or obese people.

BACKGROUND

Description of the condition

The prevalence of overweight and obesity is increasing worldwide across different age groups (Kleinert 2015; Lobstein 2015). According to the World Health Organization (WHO), the prevalence of obesity doubled between 1980 and 2008 and it is increasing more rapidly in lower- and middle-income countries (WHO 2010). In the adult population, obesity is currently more prevalent in women than in men; between 23% and 29% of women are obese in the European, Eastern Mediterranean and American regions (Yatsuya 2014). Obesity can lead to high blood pressure, heart disease, stroke, diabetes and insulin resistance (WHO 2010). A systematic review of 23 trials reporting national data on adolescent obesity shows that in 21 countries the prevalence of overweight and obesity was higher than 20% (Bibiloni 2013). The prevalence of overweight and obesity in children has shown a remarkable increase over recent decades, representing a public health challenge as this prevalence tends to track into adult life (Dietz 2004; Mahoney 1991). A systematic review of the economic burden of obesity worldwide estimated that compared to normal weight individuals, those who are obese have 30% greater medical costs (Withrow 2011). Moreover, it has been estimated that every kilogram of weight gain during adulthood increases the risk of cardiovascular disease by 3.1% to 5.7% (Anderson 2001).

Description of the intervention

Calcium is the most abundant mineral in the human body. It is available in estimated quantities of 1.2 kg. Ninety-nine per cent of calcium is found as calcium hydroxyapatite in the skeletal system and is essential for this system's creation, rigidity and maintenance (Bauer 2013). The remaining one per cent is distributed between

the intra- and extracellular fluids where it is involved in the majority of the metabolic processes as well as in muscle contraction, nervous system transmission, enzymatic activation, and hormonal function (Heaney 2006). Calcium metabolism acts over the 0.1% located in the extracellular fluid. Calcium serum levels are regulated by the parathyroid hormone, vitamin D, and calcitonin. All of these control calcium bowel absorption, its bone resorption and renal excretion (NIH 1994).

Calcium requirements are high during all stages of life (Heaney 2006). Dietary recommendations for individuals over 19 years of age vary from 100 mg to 1300 mg, depending on the reference guidelines (IOM 2011; WHO 2010).

In most low- and middle-income countries, daily calcium intake is well below recommendations; however, low intakes are also observed in special age groups, such as adolescents, in high-income countries (IOM 1997). Whereas calcium intake seems to be below 600 mg a day in low- and middle-income countries, reports from high-income countries show that the intake is above 900 mg a day depending on age groups (Bauer 2013). A review of studies reporting dietary intakes of pregnant women from low- and middle-income countries shows consistently low calcium intakes across Asian, African and Latin American countries (Lee 2013).

Interventions, such as calcium supplementation or food fortification, have been used for many years as strategies to increase calcium intake. Calcium supplementation is currently recommended by the WHO during pregnancy for the improvement of maternal and infant outcomes (WHO 2013). Calcium supplements are frequently consumed in high-income countries; however reports show that this is an uncommon practice in low- and middle-income countries (Bauer 2013).

There is some evidence of an inverse relationship between calcium intake and body weight (Zemel 2001). A systematic review found that among overweight or obese individuals, calcium supplementation compared to placebo produced a mean body weight loss of 0.7 kg (95% confidence interval (CI) -1 to -0.5) (Onakpoya 2011). Six of the included trials had a duration of six months with a dose of 1000 mg of elemental calcium per day while one trial had a duration of 24 months with a dose of 1500 mg of elemental calcium per day . The clinical relevance of this reduction has been questioned. However, at a population level, a small effect could help prevent the observed global trends (Heaney 2011).

Adverse effects of the intervention

Calcium intake upper limits are between 2000 mg to 3000 mg daily depending on the age group, according to the Institute of Medicine (IOM 2011).

The following adverse events have been described for high calcium intakes:

Cardiovascular diseases

Several trials have shown an inverse association between calcium intake and blood pressure or hypertension (Cormick 2015; Entezari 2015). However, a secondary analysis of a trial designed to assess the effect of calcium supplementation on bone mineral density among postmenopausal women described a higher risk of self-reported myocardial infarction among those who received calcium supplements (Bolland 2008). The results of this secondary analysis have been questioned, as the change in risk was no longer significant when the analysis was limited to data that could be verified by hospital records (Sabbagh 2009). A recent review concluded that there is no firm evidence that calcium supplementation increases the risk for coronary heart disease or the all-cause mortality risk in elderly women (Lewis 2015). The review highlights that self-reported myocardial infarction should not be used as the primary outcome in randomised controlled trials (RCTs) of calcium supplementation, as it can be confused with gastrointestinal symptoms (Lewis 2012).

Gastrointestinal symptoms

A review showed an increased rate of self-reported gastrointestinal events in participants receiving calcium compared with placebo (relative risk (RR) 1.43 (1.28 to1.59); Lewis 2012).The gastrointestinal events reported were acute abdominal pain, indigestion and constipation. No relationship to the calcium salt formulation or dose was reported.

Nephrolithiasis

There is some controversy as to whether increasing calcium intake reduces or increases the risk of kidney stone formation. One proposed explanation is that the effect depends on the basal dietary calcium intake. Calcium in the intestine binds to potential stone formation factors such as oxalates, which restrict its absorption and reduce the risk of stone formation (Heaney 2006). However, after this binding is saturated, higher calcium intakes do not produce further benefits. One RCT of calcium supplementation of 1000 mg a day combined with vitamin D showed an increased risk of kidney stones in the intervention group, however intakes in this group were higher than calcium recommended intakes as baseline mean calcium intake was 1148 mg ± 654 mg a day (Jackson 2006). Another RCT evaluating men with a history of kidney stones, allocated to receive either a high or low calcium diet, showed a 50% decrease in the recurrence of kidney stone formation (Borgui 2002).

Iron deficiency anaemia

Calcium supplementation has been linked with impaired iron absorption; however, the long-term effect of calcium supplementa-

tion on iron status has been questioned (Abrams 2001; Gaitán 2011; Harris 2002; Kalkwarf 1998; Mølgaard 2005; Yan 1996).

How the intervention might work

Three mechanisms by which calcium could affect body weight have been postulated. The first is linked to the regulation of the parathyroid hormone that is required to maintain calcium concentrations in extracellular fluids (Centeno 2009; Zemel 2009). Serum calcium is tightly regulated and small reductions stimulate parathyroid hormone and 1-25 vitamin D secretion to produce an increase of calcium resorption from the bones, reabsorption from the kidneys, and absorption in the intestine. However, high levels of parathyroid hormone and 1-25 vitamin D also stimulate calcium influx into different cell types (Zemel 2001). In the adipocyte, this increase of intracellular calcium stimulates fatty acid synthetase and lipogenesis (Zemel 2009). Low calcium diets have also been linked to insulin resistance and high blood pressure through similar collateral effects of increased parathyroid levels (Heaney 2006). A second postulated mechanism is related to appetite regulation. Higher calcium intakes have been linked to an increase of glucagon‐like peptide‐1 that reduces appetite (Gonzalez 2014). A third mechanism is associated with the reduction of fatty acid absorption in the intestine. Higher calcium intakes could bind to bile acids or to fatty acids impairing their absorption and decreasing available energy (Boon 2007; Vaskonen 2003).

Why it is important to do this review

A decline in calcium intake has been observed to be associated with an increase in population weight gain (Davies 2000). On a population level, a small decrease in body weight could help reverse the trend of increased weight gain. A systematic review found that calcium supplementation compared to placebo reduces weight by 0.7 kg (95% CI 0.5 to 1; Onakpoya 2011) in overweight or obese people. Another systematic review found that calcium supplementation compared to placebo reduces weight by 0.4 kg (CI 0.3 to 1.1) in the general population (Trowman 2006). Several trials have been published since these reviews. In our review, we will include trials with overweight and obese individuals.

OBJECTIVES

To assess the effects of calcium supplementation for weight reduction in overweight or obese people.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials (RCTs).

Types of participants

We will include overweight or obese participants of any age or sex. Pregnant women will also be included.
We will classify participants as being overweight or obese using the body mass index (BMI), which is a person's weight divided by the square of the person's height (kg/m^2).

Diagnostic criteria for overweight and obesity

Adults: overweight BMI $\geq$ 25 to < 29.9, obesity BMI $\geq$ 30 (WHO 2000).
Children and adolescents: we will accept validated classifications for overweight or obese children or adolescents such as the World Health Organization (WHO) child growth standards for 0 to 60 months, WHO growth references for school aged children and adolescents using BMI for age (de Onis 2007; WHO 2007), the International Obesity Task Force child BMI cut offs that are derived from BMI centiles at 18 years, and BMI z scores.
Changes in diagnostic criteria may produce significant variability in the clinical characteristics of the participants included as well as in the results obtained (which will be investigated through subgroup analysis) (Cole 2012).

Types of interventions

We plan to investigate the following comparisons of intervention versus control/comparator.

Intervention

(a) Oral calcium supplementation
(b) Calcium food or beverage fortification

Comparator

- Placebo compared with (a) or (b)
- Non-calcium fortified food or beverage compared with (b)

Calcium fortification could include salt of calcium carbonate, sulphate, citrate, citrate malate, chloride, hydroxyapatite, phosphate, acetate, lactate, glycerophosphate, gluconate, oxide or hydroxide. Calcium content in these salts varies from 9% to 70% (Allen 2006).
Concomitant interventions will have to be the same in both the intervention and comparator groups to establish fair comparisons.

Minimum duration of intervention

We will only consider RCTs in which the intervention had a minimum duration of two months.

Specific exclusion criteria

We will exclude trials of participants with chronic illnesses that affect calcium absorption or metabolism, such as lactose intolerance, inflammatory bowel disease (Crohn's disease, ulcerative colitis) or bariatric surgery patients (Peterlik 2009).

Types of outcome measures

We will not exclude trials because one or several of our primary or secondary outcome measures were not reported in the publication. In case none of our primary or secondary outcomes was reported, we will not include this trial but provide some basic information in an additional table.

Primary outcomes

- Body weight.
- Health-related quality of life.
- Adverse events.

Secondary outcomes

- Anthropometric measures other than body weight.
- All-cause mortality.
- Morbidity.
- Socioeconomic effects.

Method and timing of outcome measurement

- Body weight (kg) measured at month 2, 6, 12 or more.
- Health-related quality of life: evaluated by a validated instrument such as the Center for Disease Control and Prevention health-related quality of life questionnaire and measured at month 2, 6, 12 or more.
- Adverse events: defined as total incidence of adverse events occurring at any time after initiation of the intervention. Specific adverse events will be specified as incidence of:
    - Hypercalcaemia: defined as the proportion of participants who have a serum calcium level above the upper limit of 10 mg/dL (Shane 2006).
    - Hypercalciuria: defined as the proportion of participants who have a 24-hour urine collection of calcium > 250 mg in women and > 300 mg in men (Hodkinson 1958) or > 4 mg/kg in both sexes (Coe 1977).
    - Nephrolithiasis: defined as the proportion of participants who experience a kidney stone clinically or radiologically.
    - Coronary heart disease (CHD): including myocardial infarction, angina pectoris and acute coronary syndrome, and chronic CHD verified by clinical review, hospital record, or death certificate.
    - Secondary hyperparathyroidism: assessed by parathyroid hormone levels above the upper limit of 65 pg/mL (Eastell 2014)
    - Anaemia: measured by serum haemoglobin levels below 110 g/L in children 6 to 59 months of age and pregnant women; 115 g/L in children 5 to 11 years of age; 120 g/L in children 12 to 14 years of age and non-pregnant women and 130 g/L in men (WHO 2011).
    - Gastrointestinal symptoms: defined as the proportion of participants who experience constipation, anorexia, nausea, vomiting, or epigastric pain.
- Anthropometric measures other than body weight: defined as body mass index (BMI) and waist circumference at month 2, 6, 12 or more.
- All-cause mortality: defined as death from any cause, occurring at any time after initiation of the intervention.
- Morbidity: defined as diabetes, CHD or stroke diagnosed at any time after initiation of the intervention.
- Socioeconomic effects: such as direct costs defined as admission/readmission rates, average length of stay, visits to general practitioner, accident/emergency visits, medication consumption at month 2, 6, 12 or more; indirect costs: defined as resources lost due to illness by the participant or their family member at month 2, 6, 12 or more.

Summary of findings

We will present a 'Summary of findings' table to report the following outcomes, listed according to priority.

1. Body weight.
2. Health-related quality of life.
3. Adverse events.
4. All-cause mortality.
5. Morbidity.
6. Socioeconomic effects.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception of each database to the specified date and will place no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL).
- MEDLINE.
- EMBASE.

- LILACS.
- ClinicalTrials.gov.
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Protal (http://apps.who.int/trialsearch/).

We will continuously apply a MEDLINE (Ovid SP) email alert service established by the Cochrane Metabolic and Endocrine Disorders (CMED) Group to identify newly published trials using the same search strategy as described for MEDLINE (for details on search strategies, see Appendix 1). After supplying the final review draft for editorial approval, the CMED Group will perform a complete updated search on all databases available at the editorial office and will send the results to the review authors. Should we identify new trials for inclusion, we will evaluate these, incorporate the findings into our review, and resubmit another review draft (Beller 2013).

If we detect additional relevant key words during any electronic or other searches, we will modify the electronic search strategies to incorporate these terms and will document the changes.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. In addition we will contact authors of included trials to identify additional information on the retrieved trials and, if further trials exist, trials that we may have missed.

Data collection and analysis

Selection of studies

Two review authors (GC, NM) will independently scan the abstract, title, or both, of every record we retrieve in the literature searches, to determine which trials we should assess further. We will obtain the full-text of all potentially relevant records. We will resolve any disagreements through consensus or by recourse to a third review author (AC). If we cannot resolve a disagreement, we will categorise the trial as a 'study awaiting classification' and contact the trial authors for clarification. We will present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to show the process of trial selection (Liberati 2009).

Data extraction and management

For trials that fulfil inclusion criteria, two review authors (GC, NM) will independently extract key participant and intervention characteristics. We will report data on efficacy outcomes and adverse events using standard data extraction sheets from the CMED Group. We will resolve any disagreements by discussion or, if required, by consultation with a third review author (AC).

We will provide information about potentially relevant ongoing trials including trial identifier in the 'Characteristics of ongoing trials' table and in a joint appendix 'Matrix of trial endpoint (publications and trial documents)'. We will try to find the protocol for each included trial and will report primary, secondary and other outcomes in comparison with data in publications in a joint appendix.

We will email all authors of included trials to enquire whether they would be willing to answer questions regarding their trials. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the trial from the primary author(s) of the article, if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we will maximise the information yield by collating all available data and will use the most complete dataset aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary trial and trial documents of included trials (such as trial registry information) as secondary references under the study identifier(ID) of the included trial. Furthermore, we will also list duplicate publications, companion documents, multiple reports of a trial and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trial registers

In case data of included trials are available as study results in clinical trial registers such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract data. If there is also a full publication of the trial, we will collate and critically appraise all available data. If an included trial is marked as a completed study in a clinical trial register but no additional information (study results, publication or both) is available, we will add this trial to the table 'Characteristics of studies awaiting classification'.

Assessment of risk of bias in included studies

Two review authors (GC, NM) will independently assess the risk of bias of each included trial. We will resolve any disagreements by consensus, or by consultation with a third review author (AC). In cases of disagreement, we will consult the rest of the group and make a judgement based on consensus. If adequate information is not available from trial authors, trial protocols or both we will contact trial authors for missing data on 'Risk of bias' items.

We will use the Cochrane 'Risk of bias' assessment tool (Higgins 2011a; Higgins 2011b) and will judge 'Risk of bias' criteria as having either low, high, or unclear risk. We will evaluate individual

bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein (Higgins 2011a).

Random sequence generation (selection bias due to inadequate generation of a randomised sequence) - assessment at trial level

For each included trial we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the trial. We will consider the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment) - assessment at trial level

We will describe for each included trial the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We will also evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014). Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we will distinguish between studies we rate as at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies we rate as at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We will re-classify judgements of unclear, low or high risk of selection bias as specified in Appendix 2.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial) - assessment at outcome level

We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel is ensured, and it is unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment) - assessment at outcome level

We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement is likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data) - assessment at outcome level

For each included trial and or each outcome, we will describe the completeness of data, including attrition and exclusions from the analyses. We will state whether the trial reported attrition and exclusions, and the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We will also note if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We will consider the implications of missing outcome data per outcome such as high drop-out rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically-relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes is not enough to have a clinically-relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically-relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting) - assessment at trial level

We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to ORBIT classification' (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting.

- Low risk of bias: the trial protocol is available and all of the trial's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is unavailable, but it is clear that the published reports include all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all of the trial's pre-specified primary outcomes are reported; one or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane review are reported incompletely so that we cannot enter them in a meta-analysis; the trial report fails to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

Other bias (bias due to problems not covered elsewhere) - assessment at trial level

- Low risk of bias: the trial appears to be free of other sources of bias.
- Unclear risk of bias: there is insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial has a potential source of bias related to the specific trial design used; the trial has been claimed to have been fraudulent; or the trial had some other serious problem.

We will present a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We will distinguish between self-reported, investigator-assessed and adjudicated outcome measures.

We will accept the following outcomes as self-reported.

- Adverse events as reported by participants.
- Health-related quality of life.
- Body weigh as measured by participants.
- Anthropometric measures other than body weight as measured by participants.
- Socioeconomic effects as reported by participants.

We will require the following outcomes as investigator-assessed.

- Body weight as measured by trial personnel.
- Adverse events as measured by trial personnel.
- Anthropometric measures other than body weight as measured by trial personnel.
- All-cause mortality.
- Morbidity.

- Socioeconomic effects as measured by trial personnel.

Summary assessment of risk of bias

Risk of bias for a trial across outcomes: some risk of bias domains like selection bias (sequence generation and allocation sequence concealment) affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, all endpoints investigated in the associated trial will be marked as 'high' risk. Otherwise, we will not perform a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains: we will assess the risk of bias for an outcome measure including all of the entries relevant to that outcome, i.e. both trial-level entries and outcome-specific entries. 'Low' risk of bias is defined as low risk of bias for all key domains, 'unclear' risk of bias as unclear risk of bias for one or more key domains and 'high' risk of bias as high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains: these are our main summary assessments that will be incorporated in our judgements about the quality of evidence in the 'Summary of finding' tables. 'Low' risk of bias is defined as most information coming from trials at low risk of bias, 'unclear' risk of bias as most information coming from trials at low or unclear risk of bias and 'high' risk of bias as a sufficient proportion of information coming from trials at high risk of bias.

Measures of treatment effect

Dichotomous data

When at least two trials are available for a comparison and a given outcome we will express dichotomous data as odds ratio (OR) or risk ratio (RR) with 95% confidence interval (CI).

Continuous data

We will calculate mean differences (when trials use the same measure) or standardised mean differences (SMDs) (when trials use different measurement scales) and 95% CIs for continuous outcome measures. When necessary, we will calculate effect estimates from P values, t statistics or other available statistics. For those studies which provide only change scores, we will perform separate analyses to those studies which provide only final values. We will combine both values using the generic inverse variance method (Higgins 2011a).

Time-to-event data

We will express time-to-event data as hazard ratio with 95% CI.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome. If more than one comparison from the same trial is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants do not contribute multiply (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2011a).

We will attempt to reanalyse cluster randomised trials that have not appropriately adjusted for potential clustering of participants within clusters in their analysis.The variance of the intervention effects will be inflated by a design effect (DEFF). Calculation of a DEFF involves estimation of an intra-cluster correlation (ICC). Estimates of ICCs will be obtained through contact with authors, or imputed using estimates from other included studies that report ICCs, or using external estimates from empirical research (e.g. Bell 2013). We plan to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we will obtain missing data from trial authors and will carefully evaluate important numerical data such as screened, randomly-assigned participants as well as intention-to-treat, and as-treated and per-protocol populations. We will investigate attrition rates (e.g. drop-outs, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and imputation methods (e.g. last observation carried forward).

In trials where the standard deviation (SD) of the outcome is not available at follow-up, or cannot be recreated, we will standardise by the average of the pooled baseline SD from those trials in which this information was reported.

Where means and SDs for outcomes have not been reported and we have not received the needed information from trial authors, we will impute these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005). We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we will report per outcome which trials were included with imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report trial results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we will

also consider the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); where an I^2 statistic $\geq$ 75% indicates a considerable level of heterogeneity (Higgins 2011a).
When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

If we include 10 or more trials investigating a particular outcome, we will use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. Therefore we will interpret results carefully (Sterne 2011).

Data synthesis

We plan to undertake (or display) a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across trials, we will primarily summarise low risk of bias data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration to the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1% we will use Peto's odds ratio method, provided that there is no substantial imbalance between intervention and comparator group sizes and intervention effects are not exceptionally large. In addition, we will also perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Quality of evidence

We will present the overall quality of the evidence for each outcome specified under Types of outcome measures: Summary of findings' according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (GC, NM) will independently rate the quality of evidence for each outcome. We will present a summary of the evidence in a 'Summary of findings' table. This will provide key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome and rating of overall confidence in effect estimates for each outcome. We will create the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* by means of Review Manager (RevMan)'s table editor (RevMan 2014). We will include an appendix titled 'Checklist to aid consistency and reproducibility of GRADE assessments' (Meader 2014) to help with standardisation of the 'Summary of findings' tables (Higgins 2011a). Alternatively, we will use the GRADEpro Guideline Development Tool (GDT) software (GRADEproGDT 2015) and present evidence profile tables as an appendix. We will present results for the outcomes as described in the Types of outcome measures section. If meta-analysis is not possible, we will present the results in a narrative format in the 'Summary of findings' table. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the Cochrane review where necessary.

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and plan to carry out the following subgroup analyses with investigation of interactions.

- Menopausal status: pre- and post-menopausal women.
- Age: children, adults, older adults.
- Sex.
- BMI: obese, overweight.
- Physical activity: sedentary or active.
- Calcium supplementation: low dose $\leq$ 500 mg, moderate dose 500 to 1000 mg, high dose $\geq$ 1000 mg.
- Baseline energy intake: restricted energy intake or not.
- Pregnancy status.
- Type of diet as co-intervention.

Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting the analysis to:

- Published trials.
- Taking into account risk of bias, as specified in the Assessment of risk of bias in included studies section.
- Very long or large trials to establish the extent to which they dominate the results.
- Trials using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country.

We will also test the robustness of results by repeating the analysis using different measures of effect size (RR, OR, etc) and different statistical models (fixed-effect and random-effects models).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Calcium Compounds EXPLODE ALL TREES
2. MESH DESCRIPTOR Calcium
3. calcium:TI,AB,KY
4. #1 OR #2 OR #3
5. MESH DESCRIPTOR Obesity EXPLODE ALL TREES
6. MESH DESCRIPTOR Weight Loss
7. MESH DESCRIPTOR Overweight
8. (obes* or overweight):TI,AB,KY
9. (weight ADJ (reduction? or loss?? or control or management)):TI,AB,KY
10. body weight:TI
11. body mass index:TI
12. BMI:TI
13. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

(*Continued*)

14. #4 AND #13

MEDLINE (Ovid SP)

1. exp Calcium Compounds/
2. Calcium/
3. calcium.tw.
4. or/1-3
5. exp Obesity/
6. Weight Loss/
7. Overweight/
8. (obes* or overweight).tw.
9. (weight adj (reduction? or loss?? or control or management)).tw
10. body weight.ti.
11. body mass index.ti.
12. BMI.ti.
13. or/5-12
14. 4 and 13

[15-25: Cochrane Handbook 2008 RCT filter - sensitivity max. version]

15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomi?ed.ab.
18. placebo.ab.
19. drug therapy.fs.
20. randomly.ab.
21. trial.ab.
22. groups.ab.
23. or/15-22
24. exp animals/ not humans/
25. 23 not 24
26. 14 and 25

[27: Wong 2006a*- systematic reviews filter - Spec version]*

27. cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw
28. 14 and 27
29. 26 or 28

EMBASE (Ovid SP)

1. calcium.tw.
2. exp obesity/
3. weight reduction/
4. (obes* or overweight).tw.
5. (weight adj (reduction? or loss?? or control or management)).tw
6. body weight.ti.
7. body mass index.ti.
8. BMI.ti.
9. or/2-8
10. 1 and 9

[11: Wong 2006b *"sound treatment studies" filter - SDSSGS version]*

11. random*.tw. or clinical trial*.mp. or exp treatment outcome/

(*Continued*)

12. 10 and 11
LILACS (iAHx)
(MH:"Calcium Compounds" OR MH:"Calcium" OR calcium OR calcio) AND (MH:"Obesity" OR MH:"Weight Loss" OR MH: "Overweight" OR obes$ OR overweight OR sobrepeso OR "weight reduction" OR "weight loss" OR "weight control" OR "weight management" OR peso OR masa OR massa OR IMC) + Filter "Controlled Clinical Trial"
International Clinical Trials Registry Platform (ICTRP) Search Portal (Standard search)
overweight* AND calcium OR obes* AND calcium OR weight reduction AND calcium OR weight loss AND calcium OR weight control AND calcium OR weight management AND calcium
ClinicalTrials.gov (Advanced search)
Search Terms: obese OR obesity OR overweight OR "weight loss" OR "weight reduction" OR "weight control" OR "weight management" **Interventions:** calcium

Appendix 2. Selection bias decisions

Selection bias decisions for trials reporting unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information[a]

Reported randomisation and allocation concealment methods	' Risk of bias' judgement using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable (s)	**High risk**
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable (s)	**Unclear risk**[c]

(*Continued*)

		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables[b]	Low risk
		No baseline details	**Unclear risk**
Sequence is not truly randomised, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable (s)	High risk
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited baseline details, showing balance in some important prognostic variables[b]	**Unclear risk**
		No baseline details	High risk

[a] Taken from Corbett 2014; judgements highlighted in grey indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.
[b] Details for the remaining important prognostic variables are not reported.
[c] Imbalance identified that appears likely to be due to chance

CONTRIBUTIONS OF AUTHORS

All protocol authors read and approved the final protocol draft.

DECLARATIONS OF INTEREST

GC: none known.

AC: none known.

NM: none known.

FA: none known.

JB: none known.

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Internal sources

- Institute for Clinical Effectiveness and Health Policy, Argentina.

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External sources

- No sources of support supplied

NOTES

We have based parts of the Methods and Appendix 1 sections of this Cochrane Protocol on a standard template established by the CMED Group.