Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance (Review)

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[Intervention Review]

Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance

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A B S T R A C T

Background

Diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. The risk of developing type 2 diabetes increases with age, obesity and lack of physical activity. Insulin resistance is a fundamental aspect of the aetiology of type 2 diabetes. Insulin resistance has been shown to be associated with atherosclerosis, dyslipidaemia, glucose intolerance, hyperuricaemia, hypertension and polycystic ovary syndrome. The mineral zinc plays a key role in the synthesis and action of insulin, both physiologically and in diabetes mellitus. Zinc seems to stimulate insulin action and insulin receptor tyrosine kinase activity.

Objectives

To assess the effects of zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance.

Search methods

This review is an update of a previous Cochrane systematic review published in 2007. We searched the Cochrane Library (2015, Issue 3), MEDLINE, EMBASE, LILACS and the ICTRP trial register (from inception to March 2015). There were no language restrictions. We conducted citation searches and screened reference lists of included studies.

Selection criteria

We included studies if they had a randomised or quasi-randomised design and if they investigated zinc supplementation compared with placebo or no intervention in adults with insulin resistance living in the community.

Data collection and analysis

Two review authors selected relevant trials, assessed risk of bias and extracted data.

Main results

We included three trials with a total of 128 participants in this review. The duration of zinc supplementation ranged between four and 12 weeks. Risk of bias was unclear for most studies regarding selection bias (random sequence generation, allocation concealment) and

detection bias (blinding of outcome assessment). No study reported on our key outcome measures (incidence of type 2 diabetes mellitus, adverse events, health-related quality of life, all-cause mortality, diabetic complications, socioeconomic effects). Evaluation of insulin resistance as measured by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) showed neutral effects when comparing zinc supplementation with control (two trials; 114 participants). There were neutral effects for trials comparing zinc supplementation with placebo for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (2 studies, 70 participants). The one trial comparing zinc supplementation with exercise also showed neutral effects for total cholesterol, HDL and LDL cholesterol, and a mean difference in triglycerides of -30 mg/dL (95% confidence interval (CI) -49 to -10) in favour of zinc supplementation (53 participants). Various surrogate laboratory parameters were also analysed in the included trials.

Authors' conclusions

There is currently no evidence on which to base the use of zinc supplementation for the prevention of type 2 diabetes mellitus. Future trials should investigate patient-important outcome measures such as incidence of type 2 diabetes mellitus, health-related quality of life, diabetic complications, all-cause mortality and socioeconomic effects.

P L A I N   L A N G U A G E   S U M M A R Y

Zinc supplementation for the prevention of type 2 diabetes mellitus

Review question

What are the effects of zinc supplementation compared with placebo or no treatment for the prevention of type 2 diabetes in adults with insulin resistance?

Background

Some studies have shown that zinc improves glucose levels (glycaemic control) in people with diabetes. As a consequence of diabetes long-term complications may develop, such as kidney, nerve and eye disease. Also, the risk of cardiovascular complications like heart attacks and strokes is raised. Type 1 diabetes is a form of diabetes where the body cannot produce insulin any more. The risk of developing type 2 diabetes increases with age, obesity and lack of physical activity and is characterised by an increasing inability of the body to make good use of insulin (insulin resistance). The mineral zinc plays a key role in the action of insulin and theoretically zinc supplementation used by people with insulin resistance could prevent the onset of diabetes.

Study characteristics

We included three randomised controlled studies with a total of 128 participants in this review. The duration of zinc supplementation ranged between four and 12 weeks.

Key results

No study reported on our patient-important key outcomes (new onset of type 2 diabetes mellitus, side effects, health-related quality of life, all-cause mortality, diabetic complications, socioeconomic effects). The effects of zinc supplementation are uncertain regarding insulin resistance and lipid levels in the blood (mainly cholesterol and triglycerides).

Quality of evidence

The overall quality of the included studies was unclear because study authors did not provide important information for us to judge how the studies were performed (unclear risk of bias in most cases). In addition, the number of studies and participants is low and the study authors did not investigate important outcomes such as new onset of type 2 diabetes mellitus or side effects of zinc supplementation.

Currentness of evidence

This evidence is up to date as of March 2015.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Zinc supplementation for the prevention of type 2 diabetes mellitus

Population: non-diabetic adults with insulin resistance

Settings: not specified/outpatients

Intervention: zinc supplementation

Comparison: placebo or exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or exercise	Zinc supplementation				
Incidence of type 2 diabetes mellitus	See comment	See comment	See comment	See comment	See comment	Outcome not reported
Diabetic complications	See comment	See comment	See comment	See comment	See comment	Outcome not reported
Adverse events	See comment	See comment	See comment	See comment	See comment	Outcome not reported
Health-related quality of life	See comment	See comment	See comment	See comment	See comment	Outcome not reported
All-cause mortality	See comment	See comment	See comment	See comment	See comment	Outcome not reported
Socioeconomic effects	See comment	See comment	See comment	See comment	See comment	Outcome not reported

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance (Review)

BACKGROUND

Description of the condition

This is an update of a Cochrane Review first published in the *Cochrane Library* in 2007 (Beletate 2007), which included one study that did not provide evidence on patient-important outcome measures such as incidence of new-onset type 2 diabetes (Marreiro 2006).

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased (ADA 1999). There are two major forms of diabetes: type 1 diabetes (insulin-dependent diabetes mellitus (IDDM)) and type 2 diabetes (non-insulin-dependent diabetes mellitus (NIDDM)) (ADA 1999). Type 2 diabetes mellitus, the most prevalent form of the disease, is often asymptomatic and may remain undiagnosed for many years (ADA 1998). Type 2 diabetes may be seen in children and young adults. In type 2 diabetes the pancreatic islet cells are capable of compensating insulin resistance (see below) and producing larger quantities of insulin, at least at the beginning of the disease (Chausmer 1998).

Prevalence and costs

The worldwide prevalence of diabetes has been estimated to be around 347 million people (Danaei 2011). In 2004, an estimated 3.4 million people died from consequences of high blood sugar (WHO 2009). The World Health Organization (WHO) projects that diabetes will be the 7th leading cause of death in 2030 (WHO 2011). Diabetes accounts for over EUR 77 billion (USD 98) in healthcare costs (Tracey 2003).

The risk of developing type 2 diabetes and insulin resistance

The risk of developing type 2 diabetes increases with age, obesity and lack of physical activity. Insulin resistance is a fundamental aspect of the aetiology of type 2 diabetes (Kahn 2000). The majority of people who develop type 2 diabetes are insulin resistant, a condition in which the pancreas produces insulin but the body's cells become increasingly resistant to the regular effects of insulin, which results in hyperglycaemia (Tracey 2003). Insulin resistance has been shown to be associated with atherosclerosis (Howard 1996), dyslipidaemia (Moro 2003), glucose intolerance, hyperuricaemia, hypertension (Bonora 1998), and polycystic ovary syndrome (Kahn 2000).

Insulin resistance can be measured by using the glucose clamp technique (DeFronzo 1979), which is considered the gold standard in the assessment of insulin sensitivity (Karelis 2004). However, this method is laborious, expensive and inadequate for large-scale or epidemiological studies (Bonora 2000). Matthews et al developed the Homeostasis Model Assessment (HOMA) method, which derives an estimate of insulin sensitivity by taking fasting plasma glucose and insulin concentrations into account. HOMA is supposed to evaluate insulin resistance and the function of ß-cells. Insulin resistance is calculated with the following formula: (fasting serum insulin (µU/ml) x fasting plasma glucose (mmol/L)/22.5 (Matthews 1985).

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are associated with insulin resistance. IFG and IGT refer to an intermediate metabolic stage between normal glucose homeostasis and diabetes. This stage includes individuals with fasting glucose levels equal to or greater than 110 mg/dL but lower than 126 mg/dL or after an orale glucose tolerance test with two-hour values equal to or greater than 140 mg/dL but lower than 200 mg/dL.

Description of the intervention

Every single cell in the body needs zinc for structural and energy-producing functions. Zinc is an essential trigger for many biochemical reactions and also for protein production. Zinc plays an important role in cell division, growth and repair. It helps with wound healing and maintaining a normal sense of taste and smell. Zinc works as an immune booster and can be instrumental in fighting colds, flu and other infections. Zinc is a component of more than 200 enzymes, most of them involved in protein and DNA synthesis. Zinc has beneficial effects on sex and thyroid hormones. The human body does not produce zinc on its own, so it must be obtained from outside sources. The mineral zinc can be found in both animal and plant food sources, but the richest source of zinc comes from animal food.

The daily recommended dose of zinc is 12 mg for women and 15 mg for men. Studies suggest oral supplementation of zinc sulphate from 30 mg to 200 mg per day. The effect of supplementation with zinc was assessed in 10 patients with liver cirrhosis (Marchesini 1998). The patients presented with impaired glucose tolerance and zinc deficiency. Supplementation was approximately 136 mg zinc per day. The study showed that zinc supplementation produced a significant improvement in glucose disposal. The action of zinc seemed to be related to the increased activities of insulin independent glucose transporters (Marchesini 1998).

Adverse effects of the intervention

Amounts of zinc of two or more grams per day can cause gastrointestinal irritation and vomiting (Marchesini 1998; Marreiro 2004).

How the intervention might work

Zinc ions have an insulin-like effect. A particularly sensitive target of zinc ions is protein tyrosine phosphatase 1B, a key regulator of the phosphorylation state of the insulin receptor (Haase 2005). Several studies have investigated the role of zinc status in insulin secretion and metabolism. In vitro studies show that insulin may form a complex with zinc, improving the solubility of this hormone in the pancreatic β-cells (Rossetti 1990). Moreover, the binding ability of insulin to its receptor may be increased (Rossetti 1990). Alterations in zinc concentration and distribution in tissues, as well as improvements in insulin sensitivity after supplementation with this element have been demonstrated (Marchesini 1998).

Why it is important to do this review

Given the worldwide public health relevance of type 2 diabetes mellitus any intervention thought to be associated with only minor or no adverse effects should be investigated by means of a systematic review of the available evidence.

OBJECTIVES

To assess the effects of zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised and quasi-randomised controlled clinical trials with a minimum duration of four weeks.

Types of participants

Non-diabetic adults (18 years or older) living in the community with insulin resistance.

Diagnostic criteria

Insulin resistance had to be measured by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) or the glucose clamp technique.

To be consistent with changes in the classification of and diagnostic criteria for diabetes mellitus over the years, the diagnosis should have been established using the standard criteria valid at the time of the trial commencing (for example ADA 1999; WHO 1999). Ideally, the diagnostic criteria should have been described. If necessary, we would have used the study authors' definition of diabetes mellitus. We planned to subject diagnostic criteria to a sensitivity analysis.

Types of interventions

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

Intervention

- Zinc

Comparator

- Placebo.
- No intervention.
- Another dose of zinc.

Concomitant interventions had to be the same in the intervention and comparator groups to establish fair comparisons.

Types of outcome measures

Primary outcomes

- Incidence of type 2 diabetes mellitus.
- Adverse events.

Secondary outcomes

- Insulin resistance.
- Health-related quality of life.
- All-cause mortality.
- Diabetic complications.
- Socioeconomic effects.
- Lipid levels.

Method of outcome measurement

- Incidence of type 2 diabetes mellitus: new onset of type 2 diabetes mellitus as defined by standard diagnostic criteria (such as ADA 1997; ADA 1999; ADA 2003; WHO 1980; WHO 1985).
- Adverse events: for example, diarrhoea, nausea, fatigue, gastrointestinal discomfort, anaemia.
- Insulin resistance: estimated by the HOMA-IR or the glucose clamp technique.
- Health-related quality of life: measured with a validated instrument such as the Quality of Well-Being Scale (QWB), Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), EuroQol (EQ-5D) and specific instruments such as the Diabetes Care Profile (DCP) and the Diabetes Quality of Life Measure (DQOL).
- All-cause mortality: defined as death from any cause.
- Diabetic complications: defined as hypoglycaemia, diabetic ketoacidosis, hyperosmolar hyperglycaemic state, retinopathy, coronary heart disease, nephropathy, neuropathy, stroke and amputation.
- Socioeconomic effects: such as consequences on income, wealth, education, occupation.
- Lipid levels: as measured by total cholesterol, LDL and HDL cholesterol, triglycerides and leptin concentration.

Timing of outcome measurement

We planned to collect data for all primary and secondary outcomes for any time of outcome measurement.

'Summary of findings' table

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

1. Incidence of type 2 diabetes mellitus.
2. Diabetic complications.
3. Adverse events.
4. Health-related quality of life.
5. All-cause mortality.
6. Socioeconomic effects.

Search methods for identification of studies

Electronic searches

We searched the following sources from inception to the specified date without language restriction.

- Cochrane Library (2015, Issue 3)
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Health Technology Assessment (HTA) reports
- MEDLINE (until March 2015)
- EMBASE (until March 2015)
- LILACS (until March 2015)
- International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/):
    - Australian New Zealand Clinical Trials Registry (2 March 2015)
    - ClinicalTrials.gov (2 March 2015)

- EU Clinical Trials Register (2 March 2015)
- International Standard Randomised Controlled Trial Number (ISRCTN) (2 March 2015)
- Brazilian Clinical Trials Registry (2 March 2015)
- Chinese Clinical Trial Registry (2 March 2015)
- Clinical Trials Registry - India (2 March 2015)
- Clinical Research Information Service - Republic of Korea (2 March 2015)
- Cuban Public Registry of Clinical Trials (2 March 2015)
- German Clinical Trials Register (2 March 2015)
- Iranian Registry of Clinical Trials (2 March 2015)
- Japan Primary Registries Network (2 March 2015)
- Pan African Clinical Trial Registry (2 March 2015)
- Sri Lanka Clinical Trials Registry (2 March 2015)
- The Netherlands National Trial Register (2 March 2015)
- Thai Clinical Trials Register (2 March 2015)

For detailed search strategies see Appendix 1. We continuously applied a MEDLINE (via Ovid SP) email alert service to identify newly published studies (Appendix 1). If we detected new studies for inclusion we would have evaluated these and incorporated findings in our review before submission of the final review draft (Beller 2013).

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, (systematic) reviews, meta-analyses and health technology assessment reports.

Data collection and analysis

Selection of studies

Two review authors (LFOG, MSPO) independently scanned the title or abstract of every record retrieved. We retrieved full articles for further assessment if the information given suggested that the study: 1) included patients with insulin resistance, 2) compared a zinc intervention with placebo. Where differences in opinion existed, they were resolved by a third party (RED). If resolving disagreement was not possible, we planned to add the article to those 'awaiting classification' and contact the study authors for clarification. We present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to show the process of study selection (Liberati 2009).

Data extraction and management

For studies that fulfilled the inclusion criteria, two review authors (LFOG, MSPO) independently abstracted relevant population and intervention characteristics, using standard data extraction templates as supplied by the Cochrane Metabolic and Endocrine Disorders (CMED) Group, with any disagreements to be resolved by discussion, or, if required, by a third review author (RED) (for details see Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10).

We planned to provide information including trial identifier about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' table and in a joint appendix. We attempted to find the protocol for each included study and had planned to

report primary, secondary and other outcomes in comparison with data in publications in a joint appendix 'Matrix of study endpoint (publications and trial documents)'.

We sent an email request to the authors of included studies to enquire whether they were willing to answer questions regarding their trials. Appendix 11 shows the results of this survey. Thereafter, we sought relevant missing information on the trial from the study authors 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 study, we maximised the yield of information by collating all available data. In case of doubt the publication reporting the longest follow-up associated with our primary or secondary outcomes had priority.

Assessment of risk of bias in included studies

Two review authors (LFOG, MSPO) assessed each trial independently. We resolved possible disagreement by consensus, or with consultation of a third review author in case of disagreement (RED). In cases of disagreement, we consulted the rest of the group and made a judgement based on consensus.

We used the 'Risk of bias' assessment toll of the Cochrane Collaboration (Higgins 2011a; Higgins 2011b) and evaluated the following bias criteria:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other potential sources of bias

We judged the above 'Risk of bias' criteria as 'low risk', 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We have presented a 'Risk of bias' graph and a 'Risk of bias' summary. We assessed the impact of individual bias domains on study results at endpoint and study levels.

We planned to assess outcome reporting bias by integrating the results of the appendix 'Matrix of study endpoints (publications and trial documents)' and the appendix 'Examination of outcome reporting bias' (Kirkham 2010). This analysis would have formed the basis of the judgement of selective reporting (reporting bias).

For blinding of participants and personnel (performance bias), detection bias (blinding of outcome assessors) and attrition bias (incomplete outcome data) we intended to evaluate risk of bias separately for subjective and objective outcomes (Hróbjartsson 2013). We considered the implications of missing outcome data from individual participants.

We defined the following endpoints as subjective outcomes.

- Adverse events
- Health-related quality of life

We defined the following endpoints as objective outcomes.

- Incidence of type 2 diabetes mellitus
- Diabetic complications
- All-cause mortality
- Lipid levels
- Socioeconomic effects

Measures of treatment effect

We planned to express dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We planned to express continuous data as mean differences (MDs) with 95% CIs.

Unit of analysis issues

We planned to take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data

We planned to obtain relevant missing data from authors, if feasible, and we evaluated important numerical data such as screened, eligible and randomised participants, as well as intention-to-treat (ITT), as-treated and per-protocol populations. We investigated attrition rates, for example drop-outs, losses to follow-up and withdrawals, and critically appraised issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)).

Where standard deviations for outcomes were not reported, we planned to impute these values by assuming the standard deviation of the missing outcome to be the average of the standard deviations from those studies where this information was reported. We planned to investigate the impact of imputation on meta-analyses by means of sensitivity analysis.

Assessment of heterogeneity

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

We wanted to identify heterogeneity by visual inspection of the forest plots and by using a standard Chi² test with a significance level of α = 0.1. In view of the low power of this test, we also planned to examine heterogeneity using the I² statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003), where an I² statistic of 75% or more indicates a considerable level of inconsistency (Higgins 2011a).

Had we found heterogeneity, we would have attempted to determine potential reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We planned to use funnel plots to assess small study effects, if there were at least 10 studies for a particular outcome. There can be several explanations 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. We planned therefore to interpret the results carefully (Sterne 2011).

Data synthesis

Unless there was good evidence for homogeneous effects across studies we planned primarily to summarise low risk of bias data by means of a random-effects model (Wood 2008). We planned to interpret random-effects meta-analyses with due consideration of 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 study (Riley 2011). In addition, we planned to perform statistical analyses according to the statistical guidelines referenced in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Quality of evidence

We wanted to present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity such as directness of results. Two review authors (LFOG, MSPO) would have independently rated the quality of evidence for each outcome. We planned to present a summary of the evidence in a 'Summary of findings' table, which provides 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 studies addressing each important outcome and the rating of the overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We presented results for the outcomes as described in Types of outcome measures. If meta-analysis was not possible, we planned to present the results in a narrative 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

There were insufficient data to allow for any subgroup analyses. Should sufficient data in the future permit, we plan to carry out the following subgroup analyses and plan to investigate interaction.

- Gender (female/male)
- Age (depending on data but especially older versus younger participants)
- Participants with or without comorbidities (for example, heart attack, stroke, peripheral vascular disease)
- Duration of intervention
- Different doses of zinc

Sensitivity analysis

There were insufficient data to allow for any sensitivity analyses to explore the influence of the following factors on effect size by restricting the analysis to:

- Published studies.
- Taking into account risk of bias, as specified in the 'Assessment of risk of bias in included studies' section.
- Very long or large studies to establish how much they dominate the results.

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- Studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), or country.

We also planned to test the robustness of the results by repeating the analysis using different measures of effect size (RRs, ORs etc.) and different statistical models (fixed-effect and random-effects models).
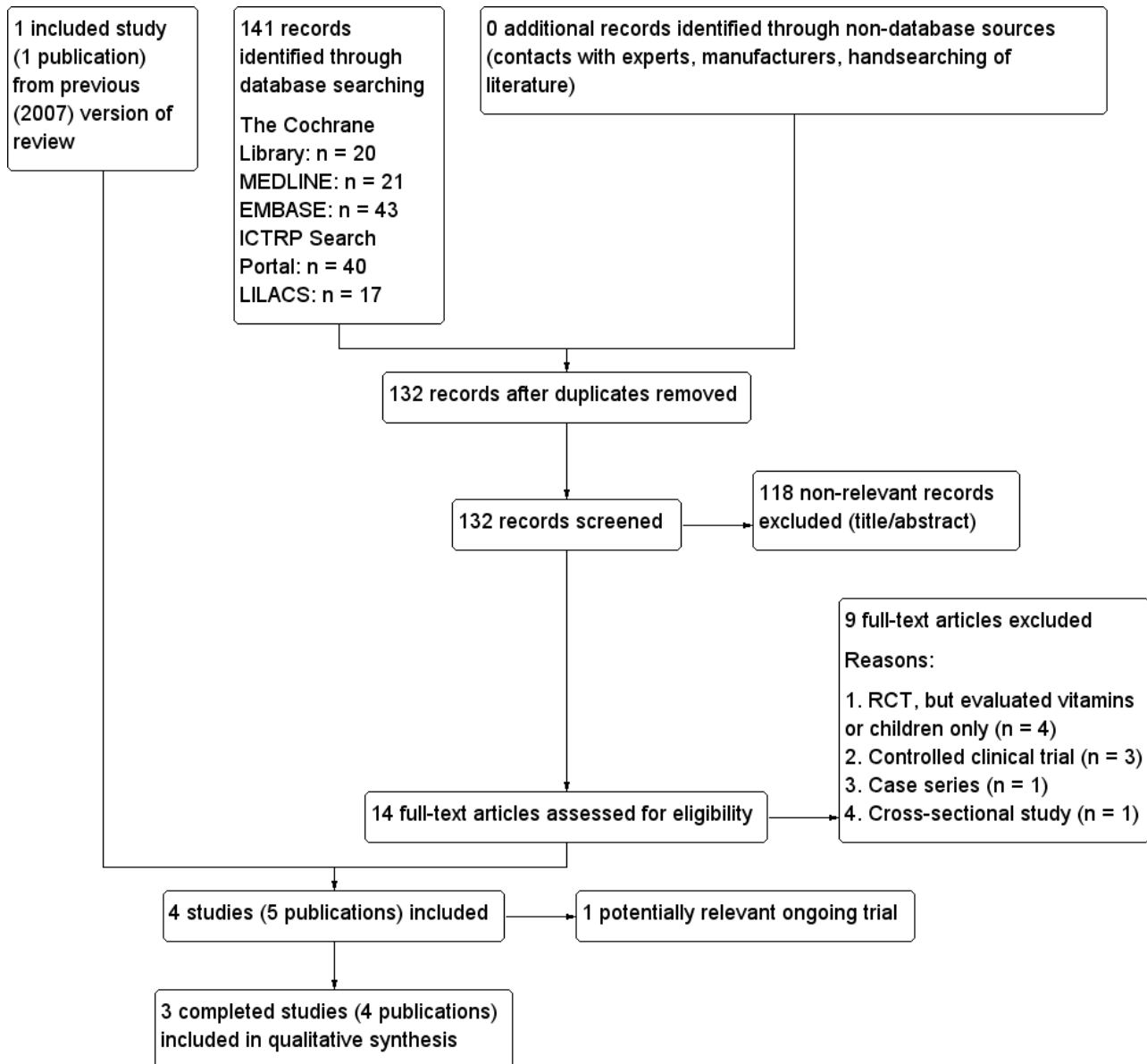
R E S U L T S

Description of studies

For a detailed description of studies, see the tables Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies.

Results of the search

In the first version of the review (2007) we evaluated 192 records. Following the assessment of the full articles, we considered only two publications for inclusion. We excluded one study (Marchesini 1998), and included one study that met our inclusion criteria (Marreiro 2006). For this first update, our comprehensive literature searches identified 132 records; from these, we identified 14 full-text publications for further examination. We excluded the other studies on the basis of their titles or abstracts, because they did not meet the inclusion criteria or were not relevant to the question under study (Figure 1). After screening the full text of the selected publications, two new studies (Gómez-García 2006; Soheilykhah 2012), and a further unpublished manuscript of Marreiro 2006 met the inclusion criteria for this update. We excluded nine studies (Czernichow 2006; Czernichow 2009; Islam 2013; Kelishadi 2010; Kim 2012; Marreiro 2002; Marchesini 1998; Ramos 2007; Stewart 2011). One further study is an ongoing trial (Ranasinghe 2013).

Figure 1. Study flow diagram.

1 included study (1 publication) from previous (2007) version of review	141 records identified through database searching: The Cochrane Library: n = 20; MEDLINE: n = 21; EMBASE: n = 43; ICTRP Search Portal: n = 40; LILACS: n = 17	0 additional records identified through non-database sources (contacts with experts, manufacturers, handsearching of literature)

132 records after duplicates removed

132 records screened → 118 non-relevant records excluded (title/abstract)

14 full-text articles assessed for eligibility → 9 full-text articles excluded

Reasons:
1. RCT, but evaluated vitamins or children only (n = 4)
2. Controlled clinical trial (n = 3)
3. Case series (n = 1)
4. Cross-sectional study (n = 1)

4 studies (5 publications) included → 1 potentially relevant ongoing trial

3 completed studies (4 publications) included in qualitative synthesis

Included studies

In this first update we included two published studies (Gómez-García 2006; Soheilykhah 2012), and a further manuscript (Marreiro 2006), in addition to the original included study (Marreiro 2002), with a total of 128 randomised participants.

Overview of study populations

The Gómez-García 2006 study enrolled 14 obese men. The Marreiro 2006 study included 56 normal glucose-tolerant obese women, while the Soheilykhah 2012 study assessed 58 overweight or obese participants with a normal oral glucose tolerance test.

Study design

All included studies claimed to be randomised controlled trials.

Settings

Two of the included studies did not report the setting where the trials were conducted (Gómez-García 2006; Soheilykhah 2012). One study involved outpatients visiting hospital clinics (Marreiro 2006).

Participants

Gómez-García 2006 evaluated 14 men between 21 and 30 years old, while Marreiro 2006 assessed 56 women aged 25 to 45 years. The mean age of participants in Soheilykhah 2012 was 38 years.

Gómez-García 2006 recruited study participants with a prediabetic state and stable weight for at least three months before the beginning of the study. Marreiro 2006 recruited glucose-tolerant obese women. Soheilykhah 2012 recruited overweight or obese participants. The mean body mass index (BMI) at baseline ranged from 31 kg/m² in Gómez-García 2006 to 36 kg/m² in Marreiro 2006. Soheilykhah 2012 evaluated 58 first degree relatives of diabetic people with a normal oral glucose tolerance test and a BMI > 25 kg/m²; the mean BMI was 29 kg/m².

Interventions

In the Gómez-García 2006 study participants received 100 mg zinc per day for four weeks (n = 7) or a matching placebo (n = 7). In the Marreiro 2006 study treatment with zinc consisted of 30 mg per day for four weeks (n = 28) or a matching placebo (n = 28). In the Soheilykhah 2012 study 28 participants received 50 mg zinc per day for 12 weeks and for 25 participants regular exercise and weight control were recommended.

Outcomes

None of the included studies investigated the incidence of type 2 diabetes mellitus, adverse events, health-related quality of life, all-cause mortality, diabetic complications or socioeconomic effects.

In the Gómez-García 2006 study the authors evaluated insulin sensitivity, leptin levels, biochemical profile and androgens. Outcome measures in the Marreiro 2006 study were insulin resistance, anthropometric parameters, diet parameters, leptin levels, insulin levels, zinc levels, lipid metabolism and fasting plasma glucose. In the Soheilykhah 2012 study adiponectin, fasting blood glucose, insulin, insulin resistance and lipid profile were assessed.

Excluded studies

Nine studies are described in the Characteristics of excluded studies (Czernichow 2006; Czernichow 2009; Islam 2013; Kelishadi 2010; Kim 2012; Marreiro 2002; Marchesini 1998; Ramos 2007; Stewart 2011). The main reason for exclusion was that the study was not a randomised controlled trial (RCT) or it was a RCT evaluating a combination of another oxidant and vitamins or included only children.

The Ranasinghe 2013 study is described in detail under Characteristics of ongoing studies. This is a RCT performed in Sri Lanka that evaluated participants in a prediabetic stage. The anticipated end of study was the end of June 2012. Participants received 20 mg zinc per day or a matching placebo for a period of 12 months. The objectives of this study were as follows: "The study aims to evaluate the effects of zinc supplementation on the progression of disease in patients with pre-diabetes from Sri Lanka and determine the metabolic effects of zinc supplementation on glycemic control. Furthermore, we aim to evaluate the effects of zinc supplementation on appetite and body weight in patients with pre-diabetes" (Ranasinghe 2013). None of our review's primary or secondary outcome measures were planned to be analysed.

Risk of bias in included studies

For details on the risk of bias of the included studies see Characteristics of included studies. For an overview of review authors' judgements about each risk of bias item for individual studies and across all 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.
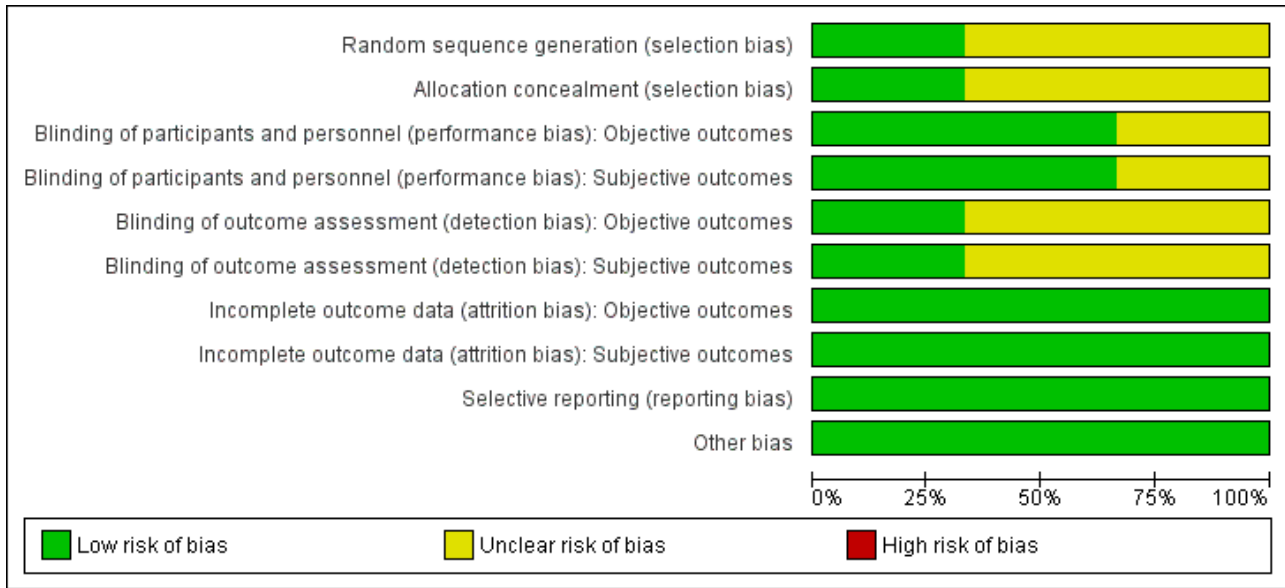
Figure 3.   'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

All included studies had an unclear risk of selection bias with the exception of Gómez-García 2006 that used opaque and sealed envelopes in a simple randomisation process.

Blinding

Two studies were double-blinded for both investigators and participants resulting in a low risk of performance bias (Gómez-García 2006; Marreiro 2006). Two of the included studies did not report on blinding of outcome assessors (Marreiro 2006; Soheilykhah 2012) and were ranked as unclear risk of bias for this domain. However, blinding of outcome assessors in Gómez-

García 2006 was done for both objective and subjective outcomes resulting in a low risk of detection bias.

Incomplete outcome data

All participants in the Gómez-García 2006 and Marreiro 2006 studies completed the trial. In the Soheilykhah 2012 study 53 of 58 participants completed the study. Altogether we ranked attrition bias as low risk for all studies.

Selective reporting

We noted no evidence of selective reporting in any of the included studies.

Other potential sources of bias

We noted no evidence of other potential sources of bias in any of the included studies.

Effects of interventions

See: Summary of findings for the main comparison

Zinc supplementation versus placebo or no intervention

Primary outcomes

Incidence of type 2 diabetes mellitus

No study reported this outcome.

Adverse events

No study reported this outcome.

Secondary outcomes

Insulin resistance

Marreiro 2006 reported neutral effects for the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), showing a mean difference (MD) of -0.10 (95% confidence interval (CI) -1.28 to 1.08), P = 0.87; 56 participants; Analysis 1.1 when comparing zinc supplementation with placebo. Soheilykhah 2012 reported a MD in the HOMA-IR of -0.27 (95% CI -1.02 to 0.48), P = 0.48; 58 participants; Analysis 2.2 for zinc supplementation versus exercise.

Health-related quality of life

No study reported this outcome.

All-cause mortality

No study reported this outcome.

Diabetic complications

No study reported this outcome.

Socioeconomic effects

No study reported this outcome.

Lipid levels

All included studies reported on this outcome (Gómez-García 2006; Marreiro 2006; Soheilykhah 2012). There were neutral effects for studies comparing zinc supplementation with placebo for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (Gómez-García 2006; Marreiro 2006) (Analysis 1.2). The one study comparing zinc supplementation with exercise, Soheilykhah 2012, also showed neutral effects for total, HDL and LDL cholesterol, and a MD in triglycerides of -30 mg/dL (95% CI -49 to -10) in favour of zinc supplementation (Analysis 2.2).

Additional parameters evaluated in the included studies

One study reported on body mass index, body perimeter, body constitution, skinfold thickness below the scapula, skinfold thickness above the hip bone, skinfold thickness of the upper arm, body mass index, waist, waist-hip ratio, energy and nutrient intake, and percentage of fat as obtained by bioimpedance (Marreiro 2006). Marreiro 2006 also measured zinc concentrations in plasma, erythrocytes and urine.

One study reported on insulin, glucose, creatinine, uric acid, leptin, testosterone and sex hormone binding globulin (Gómez-García 2006).

One study measured adiponectin, insulin and fasting blood sugar (FBS) (Soheilykhah 2012).

DISCUSSION

Summary of main results

This systematic review offers up-to-date but very limited evidence supported by only three small randomised controlled trials regarding the effects of zinc supplementation for the prevention of type 2 diabetes mellitus. The relationship between obesity and insulin resistance is seen across all ethnic groups and is evident across the full range of body weights. Insulin resistance is thought to be a major feature of type 2 diabetes, particularly since high basal plasma insulin concentrations are often found in obese type 2 diabetic people. Unfortunately, none of our patient-important outcome measures were reported in the included studies. Only parameters of insulin resistance and lipid levels were reported, showing neutral effects.

Overall completeness and applicability of evidence

None of the included studies investigated our predefined outcome measure, therefore the body of evidence is very limited. Marreiro 2006 suggested future trials with higher doses of zinc and longer follow-up intervals, since four weeks and a dose of 30 mg of zinc are not sufficient to assess a long-term process like the development of glucose intolerance and diabetes.

Quality of the evidence

The methodological quality of the included studies could not be judged according to the GRADE approach because none of our key endpoints were evaluated in the included studies.

Potential biases in the review process

Despite our thorough search in various databases we might have overlooked trials, especially with regard to the grey literature. However, we contacted the authors of the included studies to ask whether they had done another trial dealing with zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance.

Agreements and disagreements with other studies or reviews

The results of our review reflect those of the previous version of this review (Beletate 2007). Another systematic review of randomised controlled trials evaluated the effects of zinc supplementation on biomarkers of glycaemic control included type 1 and type 2 diabetic participants, participants with metabolic syndrome, participants with obesity and healthy persons (Capdor 2013). When comparing participants with metabolic conditions to healthy volunteers the study authors showed that zinc supplementation produced a greater reduction in glucose concentrations.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence on which to base the use of zinc supplementation for the prevention of type 2 diabetes mellitus.

Implications for research

There are only three included studies evaluating the effects of zinc supplementation for the prevention of type 2 diabetes mellitus. Future randomised controlled clinical trials should have standardised outcome measures, such as incidence of type 2 diabetes mellitus, insulin resistance, diabetic complications, health-related quality of life, all-cause mortality and socioeconomic outcome measures.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Gómez-García 2006

Methods	**Design:** single-centre, randomised, triple-blind, placebo-controlled clinical trial (information provided by contact with author)
	Setting: Medical Research Unit in Clinical Epidemiology, Hospital of Specialties, West National Medical Center of the Mexican Institute of Social Security, Guadalajara, Mexico (information provided by contact with author)
	Sample size: the sample size was calculated with a formula for clinical trials with a confidence level of 95% power to test a standard deviation of 80% of the euglycaemic hyperinsulinaemic clamp 0.8 mg/Kg/min and an expected difference of at least twice the standard deviation, so that a score of 6 participants per group was obtained; due to the possibility of loss during the follow-up, 7 participants were included per group

Gómez-García 2006 *(Continued)*

	Intention-to-treat analysis: "We contemplated an intention-to-treat analysis, however, no subject had to be excluded from the study" [information retrieved by contact with the study authors]
	Follow-up: 1 month
Participants	**N = 14**
	Inclusion criteria: participants included 14 obese men aged between 21 to 30 years old (body mass index (BMI) 27 kg/m²). Also, these volunteers had first degree relatives with diabetes mellitus type 2 and sustained a stable body weight for at least 3 months before the beginning of the study
	Exclusion criteria: Quote from contact with the study author by email: "The exclusion criterion was the intake of any medication with effect on the metabolism of carbohydrates, lipids, zinc, or insulin during the intervention. However, no subject had to be excluded from the study"
	Diagnostic criteria: insulin sensitivity measured by the glucose clamp method
Interventions	**Number of study centres:** 1
	Treatment before study: Quote from contact with the study author by email: "The volunteers did not ingest any treatment at least in the month preceding the study"
	Intervention and control groups: 100 mg/day of zinc sulfate orally (n = 7) versus placebo (n = 7)
Outcomes	**Outcomes reported in abstract of publication:** insulin sensitivity, leptin levels, biochemical profile and androgens
Study details	**Run-in period:** 1 month
	Study terminated before regular end (for benefit/because of adverse events): no
Publication details	**Language of publication:** Spanish
	Commercial funding/non-commercial funding/other funding: Fondo de Fomento a la Investigacion del Insituto Mexicano del Seguro Social - Fund of Scientific Support of The Mexican Institute of Social Security
	Publication status: journal article
Stated aim for study	Quote from publication: "To assess the effects of zinc sulfate on insulin sensitivity, leptin and androgens in obese individuals"
Notes	We contacted the author on 16 April 2015 to request information about risk of bias. The author kindly replied with all the information requested on 18 April 2015

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "La aleatorización de los participantes para recibir sulfato de zinc o placebo se realizó mediante el azar simple"
Allocation concealment (selection bias)	Low risk	Quote from publication: "...con la selección de un sobre cerrado que contenía la opción A o B." Quote from contact with the study author by email: "We used opaque and sealed envelopes"
Blinding of participants and personnel (performance bias)	Low risk	Quote from publication: "un ensayo clínico al azar, doble ciego, controlado con placebo"

Gómez-García 2006 *(Continued)*

Objective outcomes		Comment: the study drugs were double-blinded to both participants and investigators
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote from publication: "un ensayo clínico al azar, doble ciego, controlado con placebo" Comment: the study drugs were double-blinded to both participants and investigators
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote from contact with author by email: "The study was triple blind, the patients received one capsule of 100 mg/day of zinc sulfate orally daily or placebo capsule approved with identical presentation. Neither the researchers, nor the patients nor the person who performed the statistical analyses knew which group participants were allocated."
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote from contact with author by email: "The study was triple blind, the patients received one capsule of 100 mg/day of zinc sulfate orally daily or placebo capsule approved with identical presentation. Neither the researchers, nor the patients nor the person who performed the statistical analyses knew which group participants were allocated." Quote from contact with the study author by email: "The blinding of the outcome assessors was for both objective and subjective outcomes"
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Comment: all participants completed the study
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Comment: all participants completed the study
Selective reporting (reporting bias)	Low risk	Comment: none detected
Other bias	Low risk	Quote from contact with author by email: "There was no conflict of interest."

Marreiro 2006

Methods	**Design:** randomised, double-blind, placebo-controlled study **Setting:** outpatient (hospital clinics) **Intention-to-treat analysis:** not reported **Follow-up:** 4 weeks
Participants	**N = 56** **Inclusion criteria:** age ranging between 25 and 45 years, obesity class I and II, absence of vitamin and mineral supplementation and/or use other medication that could interfere with zinc and insulin action, nonsmokers, absence of hormone replacement therapy and/or use of oral contraceptives, and without diseases that could interfere with the nutritional status regarding zinc and insulin resistance, such as type 2 diabetes, polycystic ovary syndrome, hypertension or chronic kidney failure **Exclusion criteria:** not reported **Diagnostic criteria:** determination of insulin resistance was performed using the Homeostasis Model Assessment (HOMA) model as proposed by Matthews and co-workers

Marreiro 2006 *(Continued)*

Interventions	**Number of study centres:** 1
	Treatment before study: none
	Intervention and control groups: participants received oral zinc consisted 30 mg per day for 4 weeks (n = 28) or placebo (n = 28)
Outcomes	**Outcomes reported in abstract of publication:** BMI, fasting glucose, zinc concentration in plasma, insulin, HOMA-IR, and leptin
Study details	**Run-in period: 4** weeks
	Study terminated before regular end (for benefit/because of adverse events): no
Publication details	**Language of publication:** English
	Commercial funding/non-commercial funding/other funding: not reported
Stated aim for study	Quote from publication: "This study was conducted with the purpose to evaluating the effect of zinc supplementation on leptin levels in obese women"
Notes	There is a further unpublished manuscript reporting complementary outcomes
	We contacted the author on 16 April 2015 to request information about risk of bias. We are awaiting a reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not reported
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote from publication: "Both of the groups received pills identified by color...However, neither the researchers nor the patients knew which pill contained zinc." Comment: the study drugs were double-blinded to both participants and investigators
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote from publication: "Both of the groups received pills identified by color...However, neither the researchers nor the patients knew which pill contained zinc." Comment: the study drugs were double-blinded to both participants and investigators
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Comment: not reported
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Comment: not reported
Incomplete outcome data (attrition bias)	Low risk	Comment: all participants completed the study

Marreiro 2006 *(Continued)*
    Objective outcomes

Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Comment: all participants completed the study
Selective reporting (reporting bias)	Low risk	Comment: none detected
Other bias	Low risk	Comment: none detected

Soheilykhah 2012

Methods	**Design:** randomised clinical trial
	Setting: not reported
	Intention-to-treat analysis: not reported
	Follow-up: 12 weeks
Participants	**N = 53**
	Inclusion criteria: more than 25 years and BMI more than 25 kg/m² with normal 75 g oral glucose tolerance test
	Exclusion criteria: first degree relatives of participants who consumed vitamin D or magnesium supplementation in the past 6 months
	Diagnostic criteria: prediabetic participants
Interventions	**Number of study centres:** 1
	Treatment before study: none reported
	Intervention and control groups: 50 mg/day of oral zinc sulfate (n = 28) versus control group with regular exercise and weight control (n = 25)
Outcomes	**Outcomes reported in abstract of publication**
	Adiponectin, fasting blood glucose, insulin and insulin resistance, and lipid profile
Study details	**Run-in period:** 4 weeks
	Study terminated before regular end (for benefit/because of adverse events): no
Publication details	**Language of publication:** English
	Commercial funding/non-commercial funding/other funding: Yazd Diabetes Research Center
Stated aim for study	Quote from publication: "This study was conducted to assess the effect of zinc supplementation on serum adiponectin and insulin resistance in first degree relatives of diabetic patients."
Notes	We contacted the author on 16 April 2015 to request information about risk of bias. We are awaiting a reply

Risk of bias

Soheilykhah 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not reported
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	Comment: not reported
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Comment: not reported
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Comment: not reported
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Quote from publication: "In this randomized clinical control study 58 subjects from first degree relatives of diabetic patients...of these, 53 subjects." Comment: low attrition rate with probably only minor influence on outcome measures
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Quote from publication: "In this randomized clinical control study 58 subjects from first degree relatives of diabetic patients...of these, 53 subjects." Comment: low attrition rate with probably only minor influence on outcome measures
Selective reporting (reporting bias)	Low risk	Comment: none detected
Other bias	Low risk	Comment: none detected

BMI: body mass index
HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

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

Study	Reason for exclusion
Czernichow 2006	RCT, but evaluated vitamin C, vitamin E, ß-carotene, selenium, and zinc or placebo
Czernichow 2009	RCT, but evaluated a combination of antioxidants (vitamins C and E, ß-carotene, zinc and selenium) at nutritional doses or a placebo in metabolic syndrome
Islam 2013	Cross-sectional study

Study	Reason for exclusion
Kelishadi 2010	RCT, but only evaluated children
Kim 2012	Controlled clinical trial
Marchesini 1998	Case series study
Marreiro 2002	Controlled clinical trial and only evaluated children and adolescents
Ramos 2007	Controlled clinical trial
Stewart 2011	RCT, but evaluated vitamin B12

RCT: randomised controlled trial

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

Ranasinghe 2013

Trial name or title	**Zinc supplementation in pre-diabetes: study protocol for a randomised controlled trial**
Methods	**Design:** single-centre, randomised, double-blind, placebo-controlled clinical trial
	Setting: Faculty of Medicine, University of Colombo, Sri Lanka
	Sample size: the number of participants required for determination of a 20% reduction of fasting plasma glucose in the treatment arm in comparison with the placebo arm at 90% power and 95% confidence interval with a dropout rate of 30% is 100 patients per arm. Hence, a total of 200 participants with prediabetes will be recruited for the study
	Intention-to-treat analysis: not reported
	Follow-up: 12 months
Participants	**Inclusion criteria:** both genders between the ages of 18 and 60 years, eligible for the study through a screening test confirming the presence of prediabetes. Prediabetes is defined as the presence of fasting plasma glucose levels between 110 and 125 mg/dL or 2-hour post-oral glucose plasma glucose levels between 140 and 199 mg/dL, or both
	Exclusion criteria: on any other vitamin or mineral supplementation or the current use of a weight loss medicine or dietary modification; history of diabetes mellitus or any metabolic disease; alcohol consumption > 20 g/day; presently having acute diseases or other untreated illness requiring treatment; impaired hepatic or renal functions; lactation, pregnancy or unwillingness to use an effective form of birth control for women of child-bearing years; history or presence of any condition that would endanger the individual's safety or affect the study result
Interventions	**Number of study centres:** 1
	Treatment before study: none
	Titration period: none
	The treatment drug is a capsule containing elemental zinc 20 mg as the active ingredient; the placebo had a similar appearance, shape, weight, taste and colour as the zinc 20 mg capsule; the participants receive either 1 capsule of 20 mg zinc or an identical placebo daily, taken 1 hour before breakfast for a period of 12 months
Outcomes	**Primary outcomes:** the following biochemical assessments will be done at baseline, at stated intervals and at completion: fasting plasma glucose, oral glucose tolerance test, serum insulin,

Ranasinghe 2013 *(Continued)*

HbA1c, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and serum zinc. Furthermore, appetite will be evaluated using a visual analogue scale (VAS)

Secondary outcomes: measurement of systolic (SBP) and diastolic blood pressure (DBP), anthropometric assessment such as body weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC) and waist:hip ratio (WHR), dietary assessment using a validated food frequency questionnaire (FFQ)

Starting date	Not reported
Contact information	Dr Priyanga Ranasinghe: priyanga.ranasinghe@gmail.com
Notes	Trial registration: Sri Lanka Clinical Trial Registry: SLCTR/2012/010

HDL: high-density lipoprotein
LDL: low-density lipoprotein

DATA AND ANALYSES

Comparison 1.   Zinc supplementation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HOMA-IR	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 HOMA-IR	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Lipids	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Total cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Total cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 HDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 HDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 LDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 LDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 VLDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 VLDL lipoprotein	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Triglycerides	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 Triglycerides	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Zinc supplementation versus placebo, Outcome 1 HOMA-IR.

Study or subgroup	Zinc supplementation		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.1.1 HOMA-IR						
Marreiro 2006	28	4.3 (1.7)	28	4.4 (2.7)		-0.1[-1.28,1.08]

Zinc supplementation -10 -5 0 5 10 Placebo

Analysis 1.2. Comparison 1 Zinc supplementation versus placebo, Outcome 2 Lipids.

Study or subgroup	Zinc supplementation		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
1.2.1 Total cholesterol						
Marreiro 2006	28	192.6 (38.1)	28	184.1 (40)		8.5[-11.96,28.96]
1.2.2 Total cholesterol						
Gómez-García 2006	7	151.4 (16.7)	7	163.2 (33.1)		-11.8[-39.26,15.66]
1.2.3 HDL cholesterol						
Gómez-García 2006	7	35.1 (6.4)	7	42.8 (8.8)		-7.7[-15.76,0.36]
1.2.4 HDL cholesterol						
Marreiro 2006	28	44.1 (10.8)	28	42.7 (13)		1.4[-4.86,7.66]
1.2.5 LDL cholesterol						
Marreiro 2006	28	124.3 (34.9)	28	117.7 (34.4)		6.6[-11.55,24.75]
1.2.6 LDL cholesterol						
Gómez-García 2006	7	91.6 (16.9)	7	99.8 (41.6)		-8.2[-41.46,25.06]
1.2.7 VLDL cholesterol						
Marreiro 2006	28	23.6 (10.9)	28	23.7 (11.9)		-0.1[-6.08,5.88]
1.2.8 VLDL lipoprotein						
Gómez-García 2006	7	24.6 (6)	7	31.4 (11.1)		-6.8[-16.15,2.55]
1.2.9 Triglycerides						
Marreiro 2006	28	121.2 (51.8)	28	119.1 (59.9)		2.1[-27.23,31.43]
1.2.10 Triglycerides						
Gómez-García 2006	7	123.4 (30.2)	7	132.5 (32.1)		-9.1[-41.75,23.55]

Zinc supplementation -50 -25 0 25 50 Placebo

Comparison 2.   Zinc supplementation versus exercise

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 HOMA-IR	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Lipids	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Total cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 HDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 LDL cholesterol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Triglycerides	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Zinc supplementation versus exercise, Outcome 1 HOMA-IR.

Study or subgroup	Zinc supplementation		Regular exercise		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Soheilykhah 2012	28	1.5 (1.3)	25	1.8 (1.5)		-0.27[-1.02,0.48]

Favours zinc   -100 -50 0 50 100   Favours exercise

Analysis 2.2. Comparison 2 Zinc supplementation versus exercise, Outcome 2 Lipids.

Study or subgroup	Zinc supplementation		Exercise		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
2.2.1 Total cholesterol						
Soheilykhah 2012	28	189.5 (34.3)	25	199.8 (31)		-10.26[-27.84,7.32]
2.2.2 HDL cholesterol						
Soheilykhah 2012	28	42.6 (9.3)	25	40.3 (8.5)		2.32[-2.47,7.11]
2.2.3 LDL cholesterol						
Soheilykhah 2012	28	119.7 (24.5)	25	127.1 (21.4)		-7.35[-19.72,5.02]
2.2.4 Triglycerides						
Soheilykhah 2012	28	130.4 (34.4)	25	160.2 (37.2)		-29.85[-49.23,-10.47]

Zinc supplementation   -50 -25 0 25 50   Control group

Table 1. Overview of study populations

	Intervention(s) and comparator(s)	Sample size[a]	Screened/ eligible [N]	Ran- domised [N]	ITT [N]	Analysed [N]	Finishing study [N]	Ran- domised finishing study [%]	Follow-up time[b]
(1) Gómez- García 2006	I: 100 mg/day zinc sulfate	12 (6 partici- pants per group; 80% power)	14	7	-	7	7	100	1 month
	C: placebo			7	-	7	7	100	
	total:			14	-	14	14	100	
(2) Marreiro 2006	I: 30 mg/day zinc amino chelate	-	-	28	-	28	28	100	1 month
	C: placebo			28	-	28	28	100	
	total:			56	-	56	56	100	
(3) So- heilykhah 2012	I: 50 mg/day zinc sulfate	-	-	-	-	28	28	100	12 weeks
	C: regular exercise and weight control			-	-	25	25	100	
	total:			58	-	53	53	91.4	
Grand total	All interventions			63			63		
	All comparators			60			60		
	All interventions and comparators			128			123		

[a]According to power calculation in study publication or report

[b]Duration of intervention and/or follow-up under randomised conditions until end of study

"-" denotes not reported

C: comparator; I: intervention; ITT: intention-to-treat.

A P P E N D I C E S

Appendix 1. Search strategies

The Cochrane Library

#1 [mh Zinc/AD,AE,ST,TU,TH]
#2 (zinc near/4 supplement*):ti,ab,kw
#3 #1 or #2
#4 [mh "Glucose tolerance test"]
#5 [mh "Glucose intolerance"]
#6 [mh "Diabetes mellitus"/PC]
#7 [mh "Insulin resistance"]
#8 [mh "Metabolic syndrome X"]
#9 [mh "Prediabetic state"]
#10 (glucose near/4 (intolerance or tolerance test*)):ti,ab,kw
#11 (impaired and (fasting near/4 (glucose or glycemia* or glycaemia*))):ti,ab,kw
#12 (impaired and (glucose near/4 (toleran* or stat* or respons* or control* or regul* or metabol* or homeost*))):ti,ab,kw
#13 (reduced and (glucose near/4 (metab* or toleran*))):ti,ab,kw
#14 (praediabet* or prae diabet* or prediabet* or pre diabet*):ti,ab,kw
#15 (metabolic syndrom* or syndrome X):ti,ab,kw
#16 ((borderline or mild) near/4 diabet*):ti,ab,kw
#17 (insulin* near/4 resistan*):ti,ab,kw
#18 (((impaired or reduced) near/4 insulin) near/4 secret*):ti,ab,kw
#19 {or #4-#18}
#20 #3 and #19

MEDLINE (via Ovid SP)

---

1 (zinc adj3 supplement*).tw,ot.
2 exp Zinc/ad, ae, st, tu, th [Administration & Dosage, Adverse Effects, Standards, Therapeutic Use, Therapy]
3 1 or 2
4 exp Glucose Tolerance Test/ or exp Glucose Intolerance/
5 exp Diabetes Mellitus, Type 2/pc [Prevention & Control]
6 exp Insulin Resistance/
7 exp Metabolic Syndrome X/
8 exp Prediabetic State/
9 (glucose adj3 (intolerance or tolerance test*)).tw,ot.
10 (impaired fasting adj3 (glucose or glyc?emia*)).tw,ot.
11 (impaired glucose adj3 (toleran* or stat* or respons* or control* or regul* or metab* or homeost*)).tw,ot.
12 (reduced glucose adj3 (metab* or toleran*)).tw,ot.
13 (pr?ediabet* or pr?e diabet*).tw,ot.
14 (metabolic syndrom* or syndrome X).tw,ot.
15 ((borderline or mild) adj3 diabet*).tw,ot.
16 insulin resistan*.tw,ot.
17 ((impaired or reduced) adj3 insulin secret*).tw,ot.
18 or/4-17
19 3 and 18

[20-30: Lefebvre 2011 *RCT filter - max. sensitivity version]*

20 randomized controlled trial.pt.
21 controlled clinical trial.pt.
22 randomized.ab.
23 placebo.ab.
24 randomly.ab.
25 drug therapy.fs.
26 trial.ab.
27 groups.ab.

(Continued)
28 or/20-27
29 exp animals/ not humans/
30 28 not 29
31 19 and 30

EMBASE (via Ovid SP)

---

1 exp zinc/ae, do, dt, th [Adverse Drug Reaction, Drug Dose, Drug Therapy, Therapy]
2 (zinc adj3 supplement*).tw,ot.
3 1 or 2
4 exp glucose tolerance test/
5 exp glucose intolerance/
6 exp non insulin dependent diabetes mellitus/pc [Prevention]
7 exp insulin resistance/
8 exp metabolic syndrome X/
9 exp impaired glucose tolerance/
10 (glucose adj3 (intolerance or tolerance test*)).tw,ot.
11 (impaired fasting adj3 (glucose or glyc?emia*)).tw,ot.
12 (impaired glucose adj3 (toleran* or stat* or respons* or control* or regul* or metab* or homeost*)).tw,ot.
13 (reduced glucose adj3 (metab* or toleran*)).tw,ot.
14 (pr?e diabet* or pr?ediabet*).tw,ot.
15 (metabolic syndrom* or syndrom* X).tw,ot.
16 ((borderline or mild) adj3 diabet*).tw,ot.
17 insulin resistan*.tw,ot.
18 ((impaired or reduced) adj3 insulin secret*).tw,ot.
19 or/4-18
20 3 and 19

[21: Wong 2006 "treatment studies" filter - SDSSGS version]

21 random*.tw. or clinical trial*.mp. or exp treatment outcome/
22 20 and 21

LILACS (via IAHx)

---

zinc AND diabet*

ICTRP Search Platform (Standard search)

[searched as one string]
zinc* AND glucose OR
zinc* AND diabet* OR
zinc* AND insulin OR
zinc* AND metabol* OR
zinc* AND prediabet* OR
zinc* AND glycemia OR
zinc* AND glycaemia

Appendix 2. Description of interventions

	Intervention(s) [route, frequency, total dose/day]	Adequate[a] intervention [Yes/No]	Comparator(s) [route, frequency, total dose/day]	Adequate[a] comparator [Yes/No]

(Continued)

Gómez-García 2006	100 mg/day zinc sulfate orally	Yes	Placebo	Yes
Marreiro 2006	30 mg/day zinc amino chelate	Yes	Placebo	Yes
Soheilykhah 2012	50 mg/day zinc sulfate orally	Yes	Regular exercise and weight control	Yes

[a]The term 'adequate' refers to sufficient use of the intervention/comparator with regard to dose, dose escalation, dosing scheme, provision for contraindications and other features necessary to establish a fair contrast between intervention and comparator

	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up)	Description of participants	Study period [year to year]	Country	Setting	Ethnic groups [%]	Duration of condition [mean years (SD)]
Gómez-García 2006	I: zinc	1 month	Obese men	-	Mexico	Medical research unit	-	-
	C: placebo	(1 month)						
Marreiro 2006	I: zinc	1 month	Obese women	-	Brazil	Outpatients (hospital clinics)	-	-
	C: placebo	(1 month)						
Soheilykhah 2012	I: zinc	12 weeks	Overweight or obese participants	2009 to 2010	Iran	Yazd Diabetes Research Center	-	-
	C: regular exercise and weight control	(12 weeks)						

"-" denotes not reported

C: comparator; I: intervention; SD: standard deviation

Appendix 4. Baseline characteristics (II)

	Intervention(s) and comparator(s)	Sex [female %]	Age [mean/range years (SD), or as reported]	HbA1c [%]	BMI [mean kg/m² (SD)]	Co-medications/ Co-interventions	Comorbidities
Gómez-García 2006	I: zinc	0	21.8 (2.8)	-	30.7 (2.6)	No co-medications/co-interventions	Obesity
	C: placebo	0	25.1 (4.5)	-	30.5 (3.9)		
Marreiro 2006	I: zinc	100	35.5 (6.5)	-	35.8 (2.2)	No co-medications/co-interventions	Obesity
	C: placebo	100	33.9 (5.4)	-	36.5 (2.5)		
Soheilykhah 2012	I: zinc	57[a]	37.6 (7.4)	-	28.8 (3.5)	No co-medications/co-interventions	BMI more than 25 kg/m² with normal 75 g OGTT
	C: regular exercise and weight control						

"-" denotes not reported

[a]Refers to 53/58 participants completing the study

BMI: body mass index; C: comparator; HbA1c: glycosylated haemoglobin A1c; I: intervention; OGTT: oral glucose tolerance test; SD: standard deviation

Appendix 5. Matrix of study endpoints (publications and trial documents)

	Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a]	Endpoints quoted in publication(s)[b,c]	Endpoints quoted in <u>abstract</u> of publication(s)[b,c]
Gómez-García 2006	**Source:** N/T	**Primary outcome measure(s):** -	**Primary outcome measure(s):** -
		Secondary outcome measure(s): -	**Secondary outcome measure(s):** -
		Other outcome measure(s): Insulin sensitivity, leptin levels, biochemical profile and androgens	**Other outcome measure(s):** Insulin sensitivity, leptin levels, biochemical profile and androgens
Marreiro 2006	**Source:** N/T	**Primary outcome measure(s):** -	**Primary outcome measure(s):** -
		Secondary outcome measure(s): -	**Secondary outcome measure(s):** -
		Other outcome measure(s): BMI, fasting glucose and zinc concentration in plasma, insulin, HOMA-IR, leptin, waist circumference, waist-to-hip ratio, percentage of fat	**Other outcome measure(s):** BMI, fasting glucose, zinc concentration in plasma, urine and erythrocytes, insulin, HOMA-IR, leptin, glucose
Soheilykhah 2012	**Source:** N/T	**Primary outcome measure(s):** -	**Primary outcome measure(s):** -
		Secondary outcome measure(s): -	**Secondary outcome measure(s):** -
		Other outcome measure(s): Adiponectin, fasting blood glucose, insulin and insulin resistance and lipid profile	**Other outcome measure(s):** Adiponectin, fasting blood glucose, insulin and insulin resistance and lipid profile

- denotes not reported

[a]Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).
[b]Publication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary study).

(Continued)

cOther outcome measures refer to all outcomes not specified as primary or secondary outcome measures.

BMI: body mass index; EMA: European Medicines Agency; FDA: Food and Drug Administration (US); HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; N/A: not applicable; N/T: no trial document available

Appendix 6. Examination of outcome reporting bias according to ORBIT classification

	Outcome	High risk of bias (category A)a	High risk of bias (category D)b	High risk of bias (category E)c	High risk of bias (category G)d
Gómez-García 2006	N/A	N/A	N/A	N/A	N/A
Marreiro 2006	N/A	N/A	N/A	N/A	N/A
Soheilykhah 2012	N/A	N/A	N/A	N/A	N/A

aClear that outcome was measured and analysed; trial report states that outcome was analysed but only reports that result was not significant (Classification 'A', table 2, Kirkham 2010).

bClear that outcome was measured and analysed; trial report states that outcome was analysed but no results reported (Classification 'D', table 2, Kirkham 2010).

cClear that outcome was measured; clear that outcome was measured but not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results (Classification 'E', table 2, Kirkham 2010).

dUnclear whether the outcome was measured; not mentioned but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results (Classification 'G', table 2, Kirkham 2010).

N/A: not applicable

Appendix 7. Definition of endpoint measurement

	Incidence of type 2 diabetes mellitus	Insulin resistance	Diabetic complications	All-cause mortality	Health-related quality of life	Socioeconomic effects	Lipid levels	Severe/serious adverse events
Gómez-García 2006	N/I	Insulin sensitivity measured by the glucose clamp technique	N/I	N/I	N/I	N/I	Total cholesterol, HDL cholesterol, triglycerides measured by enzymatic methods; LDL cholesterol was estimated by the Friedewald formula and the very low density lipoproteins were calculated by triglycerides/5	N/I
Marreiro 2006	N/I	HOMA-IR	N/I	N/I	N/I	N/I	N/I	N/I
Soheilykhah 2012	N/I	HOMA-IR	N/I	N/I	N/I	N/I	Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides	N/I

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; N/I: not investigated

	Intervention(s) and comparator(s)	Participants included in analysis [N]	Deaths [N]	Deaths [%]	All adverse events [N]	All adverse events [%]	Severe/serious adverse events [N]	Severe/serious adverse events [%]
Gómez-García 2006	I: zinc	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
Marreiro 2006	I: zinc	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
Soheilykhah 2012	I: zinc	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-

"-" denotes not reported

C: comparator; I: intervention

	Intervention(s) and comparator(s)	Participants included in analysis [N]	Discontinued study due to adverse events [N]	Discontinued study due to adverse events [%]	Hospitali-sation [N]	Hospitali-sation [%]	Outpatient treatment [N]	Outpatient treatment [%]
Gómez-García 2006	I: zinc	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
Marreiro 2006	I: zinc	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-
Soheilykhah 2012	I: zinc	-	-	-	-	-	-	-
	C: placebo	-	-	-	-	-	-	-

"-" denotes not reported

C: comparator; I: intervention

Appendix 10. Adverse events (III)

	Intervention(s) and comparator(s)	Participants included in analysis [N]	Specific adverse events [description]	Specific adverse events [N participants]	Specific adverse events [% participants]
Gómez-García 2006	I: zinc	-	-	-	-
	C: placebo	-	-	-	-
Marreiro 2006	I: zinc	-	-	-	-
	C: placebo	-	-	-	-
Soheilykhah 2012	I: zinc	-	-	-	-
	C: placebo	-	-	-	-

"-" denotes not reported

C: comparator; I: intervention

Appendix 11. Survey of authors providing information on included trials

	Study author contacted	Study author replied	Study author asked for additional information [short summary]	Study author provided data [short summary]
Gómez-García 2006	16 April 2015	18 April 2015	1. Other RCT dealing with zinc and prevention of type 2 diabetes mellitus 2. Setting 3. Blinding 4. Conflict of interest 5. Exclusion criteria 6. Intention-to-treat analysis 7. Treatment before study 8. Allocation concealment	1. No 2. Medical Research Unit in Clinical Epidemiology, Hospital of Specialties, West National Medical Center of the Mexican Institute of Social Security (Guadalajara, Mexico) 3. The study was triple-blind, the participants received 1 capsule of 100 mg/day of zinc sulfate orally daily or a placebo capsule of identical appearance. Neither the researchers, nor the participants nor the person who performed the statistical analyses knew which group participants were allocated to. The blinding of outcome assessors was done for both objective and subjective outcomes 4. There was no conflict of interest 5. The exclusion criterion was the intake of any medication with an effect on the metabolism of carbohydrates, lipids, zinc, or insulin during the intervention. However, no participant had to be excluded from the study 6. An intention-to-treat analysis was contemplated, however, no participant had to be excluded from the study

(Continued)

| | | | | 7. The volunteers did not ingest any treatment at least in the month preceding the study |
| | | | | 8. Opaque and sealed envelopes |

Marreiro 2006	16 April 2015	We are awaiting a reply	N/A	N/A
Soheilykhah 2012	16 April 2015	We are awaiting a reply	N/A	N/A

N/A: not applicable; RCT: randomised controlled trial

WHAT'S NEW

Date	Event	Description
2 March 2015	New search has been performed	This review is an update of the previous Cochrane systematic review (Beletate 2007).
8 May 2014	New citation required but conclusions have not changed	The two new included studies, Gómez-García 2006 and Soheilykhah 2012, did not change our conclusions.

CONTRIBUTIONS OF AUTHORS

Regina El Dib (RED): co-ordinating the review, data management, interpretation of data, writing the review, securing funding for the review, guarantor for the review, responsible for reading and checking the review before submission.

Luis Felipe Orsi Gameiro (LFOG): undertaking manual searches, screening search results, organising retrieval of publications, screening retrieved publications against inclusion criteria, appraising quality of publications, abstracting data from publications, obtaining and screening data on unpublished studies, data management for the review, entering data into Review Manager, double entry of data.

Matheus SP Ogata (MSPO): providing additional data about publications, abstracting data from publications, obtaining and screening data on unpublished studies, entering data into Review Manager, double entry of data.

Norma SP Módolo (NSPM): responsible for reading and checking the review before submission.

Leandro G Braz (LGB): responsible for reading and checking the review before submission.

Eliane C Jorge: responsible for reading and checking the review before submission.

Paulo do Nascimento Junior (PNJ): responsible for reading and checking the review before submission.

Vânia Beletate (VB): conceiving the review.

DECLARATIONS OF INTEREST

RED: none known.

LFOG: none known.

MSPO: none known.

NSPM: none known.

LGB: none known.

ECJ: none known.

PNJ: none known.

VB: none known.

SOURCES OF SUPPORT

Internal sources

- Brazilian Cochrane Center, Brazil.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is an update of the previous Cochrane systematic review, which included one RCT (Beletate 2007).

The previous author Álvaro Atallah decided not to participate in the update of the review. For this update the following new authors contributed: Luis Felipe Orsi Gameiro, Matheus Senna Pereira Ogata, Norma Sueli Pinheiro Modolo, Leandro Gobbo Braz, Eliane C Jorge and Paulo do Nascimento Junior.

We updated the Methods section (added the 'Summary of findings' table and the new 'Risk of bias' assessment). We changed adverse events from a secondary to a primary outcome measure.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Diabetes Mellitus, Type 2 [*prevention & control]; Insulin Resistance; Randomized Controlled Trials as Topic; Zinc [*administration & dosage]

MeSH check words

Adult; Humans