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Drinking extra water or other non-caloric beverages for promoting weight loss or preventing weight gain (Protocol)

Burls A, Price AI, Cabello JB, Roberts NW

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Drinking extra water or other non-caloric beverages for promoting weight loss or preventing weight gain.
Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD012211.
DOI: 10.1002/14651858.CD012211.

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[Intervention Protocol]

Drinking extra water or other non-caloric beverages for promoting weight loss or preventing weight gain

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Editorial group: Cochrane Metabolic and Endocrine Disorders Group.
Publication status and date: New, published in Issue 5, 2016.

Citation: Burls A, Price AI, Cabello JB, Roberts NW. Drinking extra water or other non-caloric beverages for promoting weight loss or preventing weight gain. *Cochrane Database of Systematic Reviews* 2016, Issue 5. Art. No.: CD012211. DOI: 10.1002/14651858.CD012211.

ABSTRACT

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

To assess the effects of drinking extra water or other non-caloric beverages for promoting weight loss or preventing weight gain.

BACKGROUND

Obesity is increasingly common and has adverse effects on morbidity and mortality. Many people want to lose weight yet struggle to do so. In addition, public health research shows limited long-term success rates for dieting interventions (Chan 2010; Walls 2011). Observational and non-randomised intervention studies across multiple age groups suggest that there is an inverse correlation between fluid intake and weight, and as a result advice to drink extra water has been recommended as an aid to weight loss (Daniels 2011; Pan 2013; Popkin 2005; Stookey 2008).

The question of extra water intake is important for multiple reasons. When medications are used to reduce weight gain, serious side effects, such as liver, kidney and even heart problems can occur (Johansson 2009). Bariatric surgery is considered an effective treatment for obesity, however serious adverse effects may occur and operated people remain at risk for adverse events for at least one year post-intervention and at slightly elevated risk for five years (Bolen 2012; Khwaja 2010). Serious adverse outcomes may include peritonitis, scarring, ulcers, haemorrhage, gangrene and aspiration or bacterial pneumonia (Bolen 2012; Gagnon 2012). Dieters may enjoy an initial weight loss through diet and medication, however sustained weight loss is less frequent and this can reinforce a failure cycle where diets can do more harm than good (Green 2009; Haslam 2006; Walls 2011).

Description of the condition

Being obese or overweight puts physical health at risk. The World Health Organization (WHO) (WHO 2011) and NHSIC 2011 advise that excess body weight is a medical condition that may compromise health, quality of life and life expectancy. An increase in body fat normally requires energy intake to exceed energy expenditure. This means we must consume more calories than are burned in metabolic and physical activity or the balance of unused

energy will be stored as fat. NICE 2006 uses body mass index (BMI), calculated by dividing a person's weight in kilograms by the square of their height in metres, as a measure for the classification of overweight or obesity.

Excess weight, often defined as a BMI of 25 or over, is a recognised risk factor for health and is correlated with increased morbidity and mortality. International obesity rates have doubled since 1980 and it is estimated that 1.4 billion adults are overweight or obese (defined as a BMI of 30 or over) (WHO 2011). Excess weight is defined as a level of adiposity that compromises health, quality of life and life expectancy. Overweight and obesity are furtheron categorised as follows:

- Overweight: BMI 25 to 29.9 kg/m^2
- Obesity class I: BMI 30 to 34.9 kg/m^2
- Obesity class II: BMI 35 to 39.9 kg/m^2
- Obesity class III: BMI $\geq$ 40.0 kg/m^2

The WHO reports that international obesity rates have doubled since 1980. WHO estimates that 1.4 billion adults aged 20 and older are overweight; 200 million men and 300 million women are obese (BMI $\geq$30); and 40 million children under five years of age are overweight (WHO 2011). Obesity puts individuals at risk for cardiovascular disease, diabetes, organ failure, sleep apnoea, and some cancers (National Cancer Institute 2012; NICE 2006). Musculoskeletal disorders can be aggravated by excessive weight gain (Reynolds 2009). Obese individuals may endure social isolation and depression (Haslam 2006). People on certain medications can be less sensitive to cues of hunger, thirst and satiety (Kovacs 1992). Overweight and obesity describes the accumulation of body fat to the extent that impairs health although the BMI at which fat accumulation is considered unhealthy is controversial. Flegal and colleagues conducted a systematic review, which found overweight but not obese persons lived longer than ideal or underweight individuals (Flegal 2013). Moreover, there is an apparent lack of long-term success for popular diets, and an accumulation of extra weight within two years for many dieters, post-diet is reported (Chan 2010).

Description of the intervention

The intervention consists of increased water consumption, advice or encouragement to increase water consumption or increased availability of or access to water (e.g. provision of water fountains or access to bottled water). Controls will consist of usual practice defined as unchanged water consumption or availability or advice, or encouragement of consumption of a lower volume of water than in the intervention group. We will not restrict this review in terms of qualifications for personnel who administered or assisted with the intervention and in addition we will accept patient-reported outcomes. We anticipate that researchers, physicians, nutrition or diet professionals, teachers, physical activity professionals, health promotion agencies, health department staff, instructors or other institution staff could be promoting this intervention and all will be included.

Adverse effects of the intervention

Drinking large volumes of water can cause frequent or nocturnal micturition and, rarely, can lead to water toxicity and death, especially in vulnerable individuals with, for example, renal or cardiac impairment (Kovacs 1992).

How the intervention might work

Observational studies show an inverse correlation between fluid intake and weight (Pan 2013).In a non-randomised controlled interventional trial, where drinking water and education about nutrition was provided to 2^{nd} to 3^{rd} graders in selected schools and not to control schools, water consumption was higher and weight was lower in children given water and nutritional education than in those who were not (Muckelbauer 2009; Muckelbauer 2011). Drinking water could affect weight by reducing caloric intake or increasing energy use. Mechanisms by which it could reduce caloric intake include: people drinking water will be well hydrated and may be less inclined to consume caloric beverages; people who confuse thirst signals with hunger (Mattes 2010) are less likely to feel hungry; drinking water may help people to feel fuller or more satiated at meal times (Popkin 2005). Other recommendations suggest a pre-load of water before meals can reduce hunger and increase satiety (Pan 2013). A systematic review and meta-analysis found that preloading with liquids, semi-solids or solids 30 to 120 minutes before a meal resulted in fewer calories eaten during the meal. The authors report that preloads used with older obese individuals may result in greater energy reduction, however they were unable to confirm this finding without individual patient data (Almiron-Roig 2013).

Water consumption may have direct effects on hunger hormones (Clark 2013). These are defined as ghrelin, leptin, insulin, cholecystokinin (CCK) and glucagon-like peptide-1 (GPL-1). The effects are described in Mattes 2010. Ghrelin increases appetite by signalling hunger to the brain and is released primarily in the stomach. Leptin is an appetite suppressant made by fat cells. Insulin is made in the pancreas to enable the body to metabolise sugar (glucose) from carbohydrates and when there is an imbalance this can affect hunger levels. Cholecystokinin stimulates the digestion of fat and protein. GLP-1 is produced in the gut and released in response to food where it stimulates insulin secretion and inhibits glucagon secretion and this contributes to feelings of satiety (Mattes 2010). Drinking extra water may rate limit the biochemical steps needed to metabolise fat because the glycaemic and insulin index of water is zero. This simplifies the fat breakdown of free fatty acids and the transport of these free fatty acids into the mitochondria where fat is oxidised. Drinking water rather than orange juice was noted to increase fat oxidation in normal weight

individuals following a breakfast when tested on two consecutive days, even when they consumed more calories than they expended and engaged in no other intervention to reduce the calorie balance (Stookey 2012). Two days is not enough time to conclude that extra water intake is effective as a weight loss tool, however it is a promising observation.

In comparison with those who drank sweetened beverages and semi-skimmed milk, those who drank water and artificially sweetened beverages had lower ectopic fat (fat storage in non-adipose tissue) in the liver and muscle over a six-month period (Maersk 2012). The Choose Healthy Options Consciously Everyday (CHOICE) trial looked at multiple interventions and found that substituting water for high caloric beverages was a supportive compensatory strategy for weight loss (Piernas 2013). Middle-aged water drinkers were reported to have a 9% (194 kcal/d) lower caloric intake than middle-aged non-water drinkers (Dennis 2010). This population is also more likely to be on prescription medications that could make them less sensitive to cues of hunger, thirst and satiety (Daniels 2011; Kovacs 1992). Mechanisms by which drinking water could increase caloric expenditure include a direct effect on metabolic rate (Shaw 2009), as even a 1% dehydration can cause a drop in metabolic rate (Thornton 2010); or it could simply be that people who are well hydrated are more disposed to increased physical activity.

Why it is important to do this review

Obesity in the United Kingdom (UK) population continues to climb, with the Foresight report projecting obesity in over half of UK adults by 2050 (Butland 2007). The National Health Service (NHS) projects obesity-related medical costs will double by 2050 to £10 billion per year. The additional and indirect cost to society is estimated to reach £49.9 billion per year when calculated at 2015 prices (McPherson 2007). The global cost of obesity in direct and indirect costs is staggering and is estimated to be $2 trillion a year according to the 2014 McKinsey report; it will exceed the combined global costs of war, armed violence, and terrorism (Dobbs 2014). These figures, and the reality that no nation has successfully reduced population obesity, makes sustainable and successful interventions a public health priority (Lobstein 2007). Despite the large number of people trying to prevent weight gain, they struggle to do so - as can be observed in the increased global prevalence of obesity (Pietiläinen 2012). A qualitative review from Stookey 2016 reports that extra water intake was associated with a short-term decrease in energy intake, an increase in energy efficiency and increased fat absorption. The trend was sustained over time resulting in better weight management for some populations, given specific conditions. Further research is needed to confirm the observed associations and to define and optimise the interventional use of drinking extra water for weight management. If water can reduce adiposity, it is a simple, non-invasive and inexpensive alternative or addition to diets, pharmaceuticals, bariatric surgery, and physical training.

Competing interests in the diet and bottled water industry could make people vulnerable to marketing ploys by overestimating the success of dieting interventions and underestimating the danger of extreme water intake (Valtin 2002). It is prudent to establish whether additional water intake has an effect on weight, not only to know if we should advise people to drink water to help with weight control, but also because water has been used as a control intervention in diet trials (Poppitt 2011; Silver 2011). If water is effective, this makes the interpretation of such trials more challenging.Promoting water for weight reduction when it is ineffective could increase resource costs by causing a delay before people who are obese seek effective care, and could endanger vulnerable people who over-consume water (Kovacs 1992; Upadhyay 2009).

OBJECTIVES

To assess the effects of drinking extra water or other non-caloric beverages for promoting weight loss or preventing weight gain.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials (RCTs).

Types of participants

Participants of all ages, any weight, healthy or with comorbidity, with the exception of those that meet the exclusion criterion of increased fluids for other conditions, or indications such as preventing urinary tract infections, or bladder cancer.

Types of interventions

Interventions

(a) Intake of additional drinking water (or non-caloric beverages) to that consumed ad libitum.

(b) Intake of additional drinking water (or non-caloric beverages) to that consumed ad libitum at specific times, such as in the morning or before meals.

(c) Provision of, or improved access to water (or non-caloric beverages) for participants.

Comparators

- Normal fluid consumption, or drinking 120 ml or less of extra water daily, or placebo intervention not related to weight control for comparison with (a).
- Normal fluid consumption, or drinking 120 ml or less of extra water daily, or placebo intervention not related to weight control for comparison with (b).
- No improved access to water, or placebo intervention not related to weight control for comparison with (c).

We will include trials that have additional concomitant interventions that are the same in both the intervention and comparator groups.
If multiple arms are included in a trial, the arms that meet the inclusion criteria will be included in the review.

Minimum duration of intervention

We will define trial duration according to the number of weeks/months over which the interventions have been conducted and will only include trials in the analyses with interventions that last for four weeks or more.

Specific exclusion criteria

- Trials of increased fluids for other conditions or indications such as preventing urinary tract infections, or bladder cancer.
- Trials where water or other non-caloric beverages are directly substituted for or compared with caloric beverages.
- Trials where non-caloric beverages are compared with the same volume of water (as control).

Types of outcome measures

We will not exclude trials in the case that one or more of our primary or secondary outcome measures were not reported in the publication. In the case that none of our primary or secondary outcomes was reported, we will contact authors to find out if we can obtain the missing data. Where no relevant outcome data could be obtained, these trials will be reported and shown in a table.

Primary outcomes

- Weight.
- Health-related quality of life.
- Adverse events.

Secondary outcomes

- Anthropometric measures other than weight.
- All-cause mortality.
- Morbidity.
- Caloric intake.
- Satiety.
- Physical activity levels.
- Levels of hormones that affect appetite.
- Socioeconomic effects.

Method and timing of outcome measurement

- Weight: measured in kg or pounds and measured once participants were randomised to intervention/comparator groups at a minimum of at baseline, anytime during the trial and at end of the trial. All follow-up recorded post intervention will be reported.
- Health-related quality of life: evaluated by a validated instrument such as the Patient-Reported Outcomes Measurement Information System (PROMIS) and measured at a minimum of baseline and end of the trial.
- Adverse events: such as water toxicity, frequency or nocturnal micturition/incontinence and measured by event at any time after participants were randomised to intervention/comparator groups.
- Anthropometric measures other than weight: BMI, standardised BMI z-score (in children), skin-fold thickness or direct fat measurement, measured at a minimum of baseline and end of trial. All follow-up shall be reported and no minimum follow-up shall be imposed.
- All-cause mortality: defined as death and measured at any time.
- Morbidity: such as heart disease, stroke, myocardial infarction, diabetes, and measured at baseline, anytime during and at end of trial.
- Caloric intake, defined as energy intake over time. All follow-up shall be reported and no minimum follow-up shall be imposed.
- Satiety, defined as rating on numeric or visual analog scale. All follow-up shall be reported and no minimum follow-up shall be imposed.
- Physical activity levels, defined as hours of exercise weekly. All follow-up shall be reported and no minimum follow-up shall be imposed.
- Levels of hormones that affect appetite, defined as ghrelin, leptin, insulin, cholecystokinin (CCK), glucagon-like peptide 1 (GPL-1). All follow-up shall be reported and no minimum follow-up shall be imposed.
- Socioeconomic effects: such as direct costs defined as admission/readmission rates, average length of stay, visits to general practitioner, accident/emergency visits; medication consumption; indirect costs defined as resources lost due to illness by the participant or their family member.

Summary of findings

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

1. Weight.
2. Health-related quality of life.
3. Adverse events.
4. All-cause mortality.
5. Morbidity.
6. Physical activity levels.
7. Socioeconomic effects.

Search methods for identification of studies

Electronic searches

We will search the following sources from the 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.
- CINAHL.
- Science Citation Index.
- ClinicalTrials.gov (https://clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/).

We will continuously apply a MEDLINE email alert service to identify newly published studies 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, we will perform a complete updated search on all databases. Should we identify new studies 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 document the changes to the search strategy.

Searching other resources

We will try 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. We will also contact study authors of included trials to identify any further studies that we may have missed.

Data collection and analysis

Selection of studies

Two review authors (AP, AB) will independently scan the abstract, title, or both, of every record retrieved, to determine which studies we should assess further. We will investigate the full text articles of all potentially-relevant articles. We will resolve any discrepancies through consensus or recourse to the third review author (JC). If we cannot resolve a disagreement, we will categorise the study as a 'study awaiting classification' and we will contact 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 (AP, AB) will independently extract key participant and intervention characteristics. We will report data on efficacy outcomes and adverse events using standard data extraction templates supplied by the Cochrane Metabolic and Endocrine Disorders (CMED) Group. We will resolve any disagreements by discussion, or, if required, by consulting a third review author.

We will provide information (including trial identifier) about potentially-relevant ongoing studies in the 'Characteristics of ongoing studies' table and in a joint appendix. 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 'Matrix of study endpoints (publications and trial documents)'.

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 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 the case that 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 (AP, AB) will independently assess the risk of bias of each included study. We will resolve any disagreements by consensus, or by consultation with a third review author (JC). We will use the Cochrane 'Risk of bias' assessment tool (Higgins 2011a; Higgins 2011b) and will judge 'Risk of bias' criteria as either 'low', 'high', or 'unclear' risk and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) where any of the specified criteria for a judgement of 'low', unclear' or 'high' risk of bias justifies the associated categorisation.

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

We will describe for each included trial 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: sequence generation was achieved using computer random number generation or a random number table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if performed by an independent person not otherwise involved in the trial. Use of the minimisation technique will be considered 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 (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; allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocations 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 were 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 might also affect judgements on the risk of attrition bias. In case of unadjusted analyses we will distinguish between studies rated as at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies rated 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 ensured, and unlikely that the blinding could have been broken; no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial did not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to be 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 ensured, and unlikely that the blinding could have been broken; no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be 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 be 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

We will describe for each included trial, and for each outcome, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the number included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups), if reasons for attrition or exclusion where reported, 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 be introducing 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 not enough to have a clinically-relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes 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 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 (difference in means or standardised difference in means) 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 not available 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 have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) 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 review are reported incompletely so that they cannot be entered in a meta-analysis; the trial report fails to include results for a key outcome that would be expected 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 appeared to be free of other sources of bias.
- Unclear risk of bias: 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: had a potential source of bias related to the specific trial design used; has been claimed to have been fraudulent; 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 report whether weight and caloric intake were investigator-assessed or patient-reported.
We define the following outcomes as self-reported.

- Weight as reported by participants.
- Anthropometric measures others than weight, as measured by participants.
- Adverse events as reported by participants.
- Satiety as reported by participants.
- Physical activity levels as reported by participants.
- Health-related quality of life.

We define the following outcomes as investigator-assessed.

- Anthropometric measures others than weight, as measured by investigators
- Adverse events as reported by investigators.
- Levels of hormones that affect appetite.
- Morbidity.
- All-cause mortality.
- Socioeconomic effects.

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 findings' 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

We will express dichotomous data as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs). We will express continuous data as mean differences (MDs) with 95% CIs. For continuous outcomes measuring the same underlying concept (e.g. health-related quality of life) but using different measurement scales, we will calculate the standardised mean difference (SMD). We will express time-to-event data as hazard ratios (HRs) with 95% CIs.

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 (ITT), 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 (LOCF)).
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 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) through visual inspection of 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 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 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

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 contained 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 finding' 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 (AP, AB) 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 we plan to carry out the following subgroup analyses including investigation of interactions.

- Type of non-caloric beverage consumed (e.g. water, green tea) versus all other non-caloric beverages.
- Volume consumed.
- Effect in people of different levels of adiposity (normal, overweight, obese).
- Effect in different age groups (children, adults, elderly).
- Effect of timing of consumption (pre-load before meals or before different meals versus any time).
- Effects of concomitant dietary (e.g. hypo-caloric diet) or physical activity changes.

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 the following.

- 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 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 the 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 Library
#1 MeSH descriptor: [Overweight] this term only
#2 MeSH descriptor: [Obesity] this term only
#3 MeSH descriptor: [Obesity, Morbid] explode all trees
#4 MeSH descriptor: [Obesity, Abdominal] explode all trees
#5 MeSH descriptor: [Body Mass Index] explode all trees
#6 MeSH descriptor: [Energy Intake] this term only
#7 MeSH descriptor: [Eating] this term only
#8 MeSH descriptor: [Hunger] this term only
#9 MeSH descriptor: [Satiation] explode all trees
#10 MeSH descriptor: [Thermogenesis] this term only
#11 (weight next (gain or loss or lose or losing or maintain* or maintenance or change* or manage* or control* or reduc*)):ti,ab,kw (Word variations have been searched)
#12 bmi or "body mass index":ti,ab,kw (Word variations have been searched)
#13 obes*:ti,ab,kw (Word variations have been searched)
#14 overweight or "over weight" or overeat* or "over eat*":ti,ab,kw (Word variations have been searched)
#15 food intake or "energy intake":ti,ab,kw (Word variations have been searched)
#16 eating:ti,ab,kw (Word variations have been searched)
#17 hunger:ti,ab,kw (Word variations have been searched)
#18 satiety or satiation:ti,ab,kw (Word variations have been searched)
#19 fullness:ti,ab,kw (Word variations have been searched)
#20 thermogenesis:ti,ab,kw (Word variations have been searched)
#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 MeSH descriptor: [Beverages] this term only
#23 MeSH descriptor: [Mineral Waters] explode all trees
#24 MeSH descriptor: [Drinking Water] explode all trees
#25 MeSH descriptor: [Tea] explode all trees
#26 MeSH descriptor: [Teas, Herbal] explode all trees
#27 water near/5 (drink* or consumption or consume*):ti,ab,kw (Word variations have been searched)

(*Continued*)

#28 beverage* or tea or teas:ti,ab,kw (Word variations have been searched)
#29 #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 #21 and #29

MEDLINE OvidSP

1 overweight/ or obesity/ or obesity, morbid/ or Obesity, Abdominal/
2 body mass index/
3 Energy Intake/
4 Hunger/
5 Satiation/
6 Thermogenesis/
7 (weight adj (gain or loss or lose or losing or maintain* or maintenance or change* or manage* or control* or reduc*)).tw
8 obes*.ti,ab.
9 (overweight or over weight or overeat* or over eat*).tw.
10 (bmi or body mass index).tw.
11 (food intake or energy intake).tw.
12 hunger.tw.
13 (satiety or satiation).tw.
14 fullness.tw.
15 thermogenesis.tw.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 beverages/ or exp drinking water/ or mineral waters/ or exp tea/ or teas, herbal/ or teas, medicinal/
18 (water adj5 (drink* or consumption or consume*)).tw.
19 (beverage* or tea or teas).tw.
20 17 or 18 or 19
21 16 and 20
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 randomized.ab.
25 placebo.ab.
26 drug therapy.fs.
27 randomly.ab.
28 trial.ab.
29 groups.ab.
30 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31 exp animals/ not humans.sh.
32 30 not 31
33 21 and 32

EMBASE OvidSP

1 abdominal obesity/ or obesity/ or morbid obesity/
2 weight reduction/
3 food intake/ or eating/
4 energy consumption/ or caloric intake/
5 Hunger/
6 Satiation/
7 Thermogenesis/
8 (weight adj (gain or loss or lose or losing or maintain* or maintenance or change* or manage* or control* or reduc*)).tw

(*Continued*)

9 obes*.ti,ab.
10 (overweight or over weight or overeat* or over eat*).tw.
11 (bmi or body mass index).tw.
12 (food intake or energy intake).tw.
13 hunger.tw.
14 (satiety or satiation).tw.
15 fullness.tw.
16 thermogenesis.tw.
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 beverage/ or carbonated water/ or drinking water/ or herbal tea/ or mineral water/ or tea/
19 (water adj5 (drink* or consumption or consume*)).tw.
20 (beverage* or tea or teas).tw.
21 18 or 19 or 20
22 17 and 21
23 limit 22 to "therapy (maximizes sensitivity)"
24 (exp animals/ or nonhuman/) not human/
25 23 not 24

CINAHL (EBSCO Host)

1 (MH "Obesity") OR (MH "Obesity, Morbid")
2 (MH "Weight Loss")
3 (MH "Body Mass Index")
4 (MH "Energy Intake") OR (MH "Food Intake")
5 (MH "Hunger")
6 (MH "Satiation")
7 (MH "Thermogenesis")
8 TI ((weight N1 (gain or loss or lose or losing or maintain* or maintenance or change* or manage* or control* or reduc*))) OR AB ((weight N1 (gain or loss or lose or losing or maintain* or maintenance or change* or manage* or control* or reduc*)))
9 TI obes* OR AB obes*
10 TI (overweight OR "over weight" OR overeat* OR "over eat*") OR AB (overweight OR "over weight" OR overeat* OR "over eat*")
11 TI (bmi OR "body mass index") OR AB (bmi OR "body mass index")
12 TI ("food intake" OR "energy intake") OR AB ("food intake" OR "energy intake")
13 TI hunger OR AB hunger
14 TI (satiety OR satiation) OR AB (satiety OR satiation)
15 TI fullness OR AB fullness
16 TI thermogenesis OR AB thermogenesis
17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18 (MH "Tea+") OR (MH "Water+") OR (MH "Beverages")
19 TI (water N5 (drink* OR consumption OR consume*)) OR AB (water N5 (drink* OR consumption OR consume*))
20 TI (beverage* OR tea OR teas) OR AB (beverage* OR tea OR teas)
21 S18 OR S19 OR S20
22 S17 AND S21
23 S17 AND S21 Limiters - Clinical Queries: Therapy - High Sensitivity

Science Citation Index

(*Continued*)

1. TS=(bmi or "body mass index") OR TS=("food intake" or "energy intake") OR TS=(obes* OR overweight OR overeat* OR "over eat*") OR TS=("weight gain" OR "weight loss" OR "weight maintenance" or "weight change*" OR "weight management" OR "weight reduction" OR "weight control") OR TS=(thermogenesis) OR TS=(hunger or satiety or satiation or fullness) OR TS=(eating)
2. TS=(beverage* OR tea OR teas) OR TS=((water NEAR/5 (drink* OR consume* OR consumption)))
3. TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
#3 AND #2 AND #1

ClinicalTrials.gov (Advanced search)

Search Terms: overweight OR obesity OR obese OR "weight control" OR "weight reduction" OR "weight loss" OR "weight maintenance" OR "weight management" OR "weight change" OR "weight changes" OR "body mass index"
Study Type: Interventional Studies
Interventions: water OR tea OR beverage OR beverages

WHO ICTRP Search Portal (Standard search)

(to be run as one search string)
overweight AND water OR
overweight AND tea OR
overweight AND beverage* OR
obes* AND water OR
obes* AND tea OR
obes* AND beverage* OR
weight AND water OR
weight AND tea OR
weight AND beverage*

Date search conducted

Search question:
P = Overweight
I = Drinking water or non caloric beverage
O = Weight loss

Databases searched:	**Year range:**	**Number (no) records retrieved:**
CINAHL	1980 - present	
Cochrane Library	to present	
EMBASE	1974 - present	
MEDLINE	1946 - present	
Total no records retrieved:	**No duplicates removed:**	**Final total:**

Limits:
Human
Publication type: RC

(*Continued*)

Methodological filters:	
CINAHL	**RCTS:** EbscoHOST Clinical Queries: Therapy - High Sensitivity Wong 2006a
EMBASE	**RCTs** Ovid Clinical Queries: Treatment (2 or more terms high sensitivity) Wong 2006b
MEDLINE	**RCTs** Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2011 revision); Ovid format Lefebvre 2011

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**	**Ris 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]
		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

(*Continued*)

		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.

Amy I Price (AP): protocol drafting.

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Juan B Cabello (JBC): protocol drafting.

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DECLARATIONS OF INTEREST

AP: none known.

AB: none known.

JBC: none known.

NR: none known.

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.