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Low carbohydrate versus balanced carbohydrate diets for reducing weight and cardiovascular risk (Protocol)

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[Intervention Protocol]

Low carbohydrate versus balanced carbohydrate diets for reducing weight and cardiovascular risk

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ABSTRACT

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

To compare the effects of low carbohydrate weight-reducing diets to weight-reducing diets with balanced ranges of carbohydrates, in relation to changes in weight and cardiovascular risk, in overweight and obese adults without type 2 diabetes (comparison 1) and with type 2 diabetes (comparison 2).

BACKGROUND

Description of the condition

The 2017 Global Nutrition Report estimates that two billion adults worldwide are overweight or obese, and 41 million children are overweight (Development Initiatives 2017). For the first time in history, more people globally are dying from the consequences of overeating than starvation and malnutrition (Forouzanfar 2015). This shift has happened in the last 20 to 30 years and is thought to be mainly due to diets that are of poor nutritional quality, high in energy density and often ultra-processed. Such diets often result in cumulative weight gain over time and consequently increase the risk of cardiovascular disease, diabetes, stroke and some cancers (Forouzanfar 2015). Globalised food systems promote over consumption of these foods (Moubarac 2014; Swinburn 2011).

High body mass index (BMI) is an important modifiable risk factor for cardiovascular disease, diabetes, kidney diseases, certain cancers and musculoskeletal conditions (Berrington 2010; ERFC 2011; GBMRF for CD Collaboration 2014; Singh 2013; Whitlock 2009; Zheng 2011). The disease burdens related to obesity are particularly evident in low- and middle-income countries. Cardiovascular disease deaths rose by 12.5% from 15.9 million in 2005 to 17.9 million in 2015, and low- and middle-income countries accounted for over three-quarters of these deaths (GBD MCDC 2016). In Africa, between 1980 and 2014, age-standardised prevalence of type 2 diabetes increased from 4.8% to 9.7% in men and from 7.7% to 12.6% in women (NCD-RisC 2017). These shifting disease patterns have a major impact on individual and family well-being, and on economies, with large direct and indirect costs being associated with illness.

Description of the intervention

Pharmacotherapy, bariatric surgery and counselling that target diet, physical activity, and behaviour change are used to treat adult obesity (Dietz 2015). Due to the chronic and relapsing nature of obesity and its related conditions, current guidelines for the treatment of obesity recommend comprehensive management approaches that aim to achieve long-term weight reduction. This includes intensive lifestyle intervention characterised by dietary restriction, increased physical activity, and behavioural management as first-line treatment (Dietz 2015; Jensen 2014). Importantly, there is not a 'one-size-fits-all' weight-reducing diet and different diets work for different people, based on preferences and ease of adherence (Jensen 2014; Johnston 2014).

The public, families and health professionals face an often dizzying array of weight-reducing diets, many of which have been commercialised as books, seminars, diet food products, supplements and other related products. These include, but are not limited to, various versions of low carbohydrate diets (for example, Atkins diet (Atkins 1999)), low fat or so-called 'balanced diets', very low fat diets (for example, Ornish diet (Ornish 2001)), and low glycaemic diets (for example, South Beach diet (Agatston 2003)).

Nutrients are needed by the body in small (i.e. micronutrients such as vitamins and minerals) or large amounts (i.e. macronutrients) for growth, repair and optimal functioning (Lichtenstein 2005). Total daily energy intake is made up of the sum of the energy provided by the three macronutrients (i.e. carbohydrate, protein and fat). Per gram of macronutrient, carbohydrates and protein each provides about 17 kilojoules, while fat provides about 37 kilojoules (Carreiro 2016). Carbohydrates are primarily contained in grains, cereals and sugar, and in the digestive tract are broken down into glucose. Carbohydrates are the largest nutrient class, and traditionally, the greatest energy source. If energy intake exceeds energy requirements, excess carbohydrates will be mainly stored in the liver as glycogen for later use or be converted to fatty acids when glycogen stores are saturated. In contrast, if the diet contains limited amounts of carbohydrate, the liver converts fat into fatty acids and ketones to replace glucose as energy source (Paoli 2013).

Low carbohydrate diets are a broad category of weight-reducing diets and programmes that manipulate and restrict macronutrient (carbohydrate, protein, fat) intake (Astrup 2004; Bazzano 2012; Campbell 2012; Hession 2009). There are no consistent and widely accepted definitions of these diets and different descriptions are used, such as 'low carbohydrate, high protein' or 'low carbohydrate, high fat', depending on the macronutrient manipulation and focus. In practice, low carbohydrate diets are applied in different ways, but generally restrict grains, cereals and legumes, and other foods that contain carbohydrates, such as dairy, most fruit and certain vegetables. The energy required is then typically replaced with food higher in fat and protein, such as meats, eggs, cheese, butter, cream and oils - many of which are animal source foods. Some low carbohydrate diets recommend eating as desired, while others apply restrictions to total energy intake (Atkins 2011; Campbell 2012).

Conventional authorities such as the European Food Safety Authority (EFSA 2017), American Institute of Medicine Food and Nutrition Board (IOM 2005), Australian National Health and Medical Research Council together with the New Zealand Ministry of Health (NHMRC 2006), and the Nordic Council of Ministers, Nordic Committee of Senior Officials for Food Issues (NNR 2012), as well as the UK's Scientific Advisory Committee on Nutrition (SACN 2015), have recommended 45% to 65% of total energy as the appropriate carbohydrate intake for adults. Thus, some people regard low carbohydrate diets to be those with carbohydrate intakes below 45% of total energy. Some published definitions of low carbohydrate diets disregard the official recommendations, and use an upper limit of 40% of total energy from carbohydrates as indicative of a low carbohydrate diet (Frigolet 2011; Wylie-Rosett 2013). In absolute, rather than proportional terms, low carbohydrate diets have been defined as having less than 200 g of carbohydrate (Frigolet 2011), while some disagree with this liberal definition, preferring to distinguish between 'non-ketogenic low carbohydrate diets' as containing 50 g to 150 g of carbohydrates, and 'ketogenic low carbohydrate diets' (or very low carbohydrate diets) as having a maximum of 50 g of carbohydrates, with this latter variant seen by some as being more effective for weight loss (Westman 2007; Yancy 2004). Ketogenic diets are characterised by a high production of ketones in the liver as an alternative energy source, as well as high levels of ketones in the blood (ketonaemia) and urine (ketonuria) when fat or protein intake is very high and carbohydrate intake is very low (less than 50 g/day) (Paoli 2013).

Weight-reducing diets aligned with current dietary recommendations are often referred to as 'low fat diets' or 'balanced, weight-reducing diets', and will be referred to as 'balanced diets' in this review (British Dietetic Association 2013). Globally, current dietary recommendations - in terms of macronutrients, micronutrients, food choices and dietary patterns

- are generally consistent, and governmental bodies from Europe, the USA, Australia and Nordic countries recommend that 45% to 65% of total energy intake should be provided by carbohydrates, between 10% and 35% by protein and between 20% and 35% by fat (EFSA 2017; IOM 2005; NHMRC 2006; NNR 2012). There is room for flexibility within these ranges from lower to higher intakes of carbohydrate, fat and protein. These dietary recommendations are accompanied by information on 'better food' choices; improving the quality of carbohydrates (e.g. whole grains versus refined grains), protein (e.g. fish versus processed meat) and fat (e.g. olive oil versus butter); as well as on maintaining a healthy body weight by aiming to keep energy intake and energy expenditure balanced.

Nutrition recommendations are moving away from macronutrient-focused, single food and single nutrient messages towards recommendations about dietary patterns and ‘total diets’ (NICE 2014; NNR 2012; USDA 2014). This has been driven mainly by the lack of clear and consistent associations between individual nutrients (micronutrients and macronutrients) and disease risk, limitations of single nutrient trials and greater successes of 'total diet' or dietary pattern interventions.

Dietary patterns can be defined as "the quantities, proportions, variety, or combination of different foods, drinks, and nutrients (when available) in diets, and the frequency with which they are habitually consumed" (USDA 2014). Current evidence supports associations between some dietary patterns and lower risk of obesity and chronic diseases, especially type 2 diabetes, cardiovascular disease, hypertension, and certain cancers (DGAC 2015; USDA 2014). For example, systematic reviews of large long-term studies show that several dietary patterns are consistently and equally associated with a lower risk of developing type 2 diabetes in the future (Alhazmi 2014; Esposito 2014; Koloverou 2014). These dietary patterns have different macronutrient compositions, but share several common components, including fruit, vegetables, wholegrains, legumes, nuts, healthy oils, adequate proteins (such as seafood and lean meat), reduced intake of red and processed meats and sugar-sweetened beverages, and little or moderate alcohol (Ndanuko 2016; NNR 2012; USDA 2014). It has been suggested that carbohydrate avoidance and the resultant food restrictions typical of low carbohydrate diets make a dietary pattern that is nutrient- and fibre-rich, diverse and promotes good health difficult to achieve (USDA 2014).

How the intervention might work

Energy balance and body weight regulation is complex and interactive, and questions on certain components of energy balance and their interactions - especially over the longer term - are yet to be answered (Hall 2012). The first law of thermodynamics and evidence from various types of studies over the past 50 years, including randomised controlled trials (RCTs), support the view that weight loss occurs when the amount of kilojoules consumed during eating and drinking is less than the amount of kilojoules expended over weeks or months (ACC/AHA 2013 Full Report; Hall 2011; Hall 2012; Hall 2015; Jensen 2014). Thus, a plausible mechanism whereby low carbohydrate diets enable weight loss is by achieving a sustained energy deficit over time even when advice to explicitly restrict energy intake is not provided. When people eliminate and restrict carbohydrate-rich foods, they are more likely to reduce energy intake because they eat less food (Brehm 2003; Sondike 2003). Related mechanisms reported in the literature include a reduction in appetite with low carbohydrate diets possibly related to the increased intake of fat and production of ketones (Boden 2005; Nordmann 2006; Westman 2007). Since total energy intake is known to drive changes in body weight, its role must be considered when examining the effect on any diet on weight changes.

Some literature indicates that certain macronutrients may have metabolic advantages over others, more specifically that lower carbohydrate intake is more effective for weight loss, independent of energy intake (Atkins 2011; Westman 2007). However, it has been proposed that when proportions of macronutrients in the diet are changed, rapid physiological adaptations occur that aim to match metabolic fuel selection to the diet. Changes in body composition and energy expenditure may be minimised by these adaptations. In this scenario, in the shorter term, all reduced energy diets would have a similar effect on loss of body fat (Hall 2011).

Literature on low carbohydrate diets also suggest that the reduced insulin secretion resulting from a low carbohydrate diet causes greater release of adipose tissue free fatty acids, fat oxidation and energy expenditure, and increased loss of body fat compared to restricting fat intake (Ludwig 2014; Taubes 2007; Westman 2007). A study in 19 obese adults confined to a metabolic ward demonstrated that an equal kilojoule-selective reduction in dietary fat resulted in no changes in insulin secretion, fat oxidation or energy expenditure and a greater net fat loss when compared to restricting carbohydrates by the same amount, which resulted in decreased insulin secretion, increased fat oxidation and decreased energy expenditure (Hall 2015).

According to recent clinical guidelines for obesity, a high quality systematic review, a scientific report to inform dietary guidelines and a recent six-month randomised controlled feeding trial, a number of different diets may lead to weight loss over the short term if they achieve a sustained energy deficit, but some of these diets may be more advantageous than others for maintaining longer-term cardiovascular and metabolic health (DGAC 2015; Jensen 2014; Johnston 2014; Wan 2017). There is evidence that weight loss of 5% and more, or BMI reduction of at least 5%, may result in clinically meaningful improvements in cardiometabolic health following dietary regimens (Brown 2016; Truby 2006; Wald 2012; Wing 2010).

Adherence and weight maintenance

Poor dietary adherence has been regarded as one of the reasons popular and traditional dieting strategies are unsuccessful, and it is well known that adherence to nutrition counselling by study participants varies widely. Evidence from quality RCTs, systematic reviews and other study designs suggest that adherence to diets is a primary driver of weight loss success, regardless of the macronutrient composition, and may explain a considerable part of whether or not dieters are able to achieve energy deficit for weight loss (Alhassan 2008; Dansinger 2005; Hall 2011; Johnston 2014; Sacks 2009). Dietary intake is difficult to measure accurately, and fidelity of application of dietary assessment methods varies widely across studies (Shim 2014), which may introduce a lot of variation into the assessment of adherence. Consequently, data on adherence to assigned diets is often lacking in weight loss trials. Also, keeping the weight off once lost is also a considerable challenge in treating obesity, with most people tending to relapse (Dietz 2015). Indeed, a systematic review including 56 RCTs reported that dieting to lose weight is most often over weeks,

months or years, and it is challenging for most people to maintain the weight lost over the long term (Collins 2013). Thus, ease of adherence to weight-reducing diets is a key factor to consider. It is also necessary to consider the time-dependant nature of the relationship between diet and weight change when examining the effect of diets on weight change. Trials typically have different periods of follow-up, and different frequencies or intervals of study contacts and measurement. Tay 2015 indicated that changes sustained over a 12-month period reflects durability of effects over the long term.

Why it is important to do this review

The public spends considerable amounts of money and time on trying to diet, on books about diet, and on products and foods to enhance weight loss. It is therefore important to examine scientific evidence behind the claims made.

Some advocates claim low carbohydrate diets decrease cardiovascular disease and diabetes risk profiles for low carbohydrate diets: reducing triglycerides, increasing high-density lipoprotein (HDL) cholesterol and improving glycaemic control over one year (Stern 2004); improving triglycerides, HDL cholesterol and glycaemic control over four years (Wing 2010); and improving aortic stiffness over four weeks (Syed-Abdul 2018). However, the diets are not without potential side effects. These include gastrointestinal disturbances, such as flatulence, indigestion, constipation or diarrhoea over the short term (Bhardwaj 2017; Brinkworth 2009a; Saslow 2014); and increasing low-density lipoprotein (LDL) cholesterol and non-HDL cholesterol over 12 months (Brinkworth 2009b; Wan 2017). Some participants report mood disturbance and impaired ability to concentrate (Brinkworth 2009c; Halyburton 2007). Other side effects of low carbohydrate diets include lack of appetite, bad breath, headaches, muscle cramps, general weakness and hair loss (Foster 2010; Rio 2001; Yancy 2004).

A prospective cohort study and meta-analysis that combined 25-year follow-up of the Atherosclerosis Risk in Community (ARIC) data (USA) and seven other cohort studies (USA, Europe, Asia and multinational) assessed the association between carbohydrate intake and mortality (Seidelmann 2018). Findings indicate that both high and low carbohydrate diets increased mortality, with lowest risk observed among those who consumed a diet containing 50% to 55% carbohydrates. The low carbohydrate dietary patterns that favoured animal fat and protein sources were associated with higher mortality, while those that favoured plant-based foods were associated with lower mortality. Additionally, diets very high in animal source foods could pose a significant threat to environmental sustainability (Sabate 2014; Soret 2014).

The debate on effective and safe diets for treating obesity continues. Many trials and systematic reviews involving obese people (with and without comorbidities) and of varying methodological quality have assessed the effects of low carbohydrate diets on weight and other risk factors. Many show little or no clinically important difference in weight loss of up to two years follow-up. A systematic review of eight RCTs found that improvements in psychosocial outcomes occur in participants on short- and longer-term weight loss programmes, regardless of the macronutrient composition of the diet (Ghoch 2016). However, low carbohydrate weight-reducing diets continue to be widely promoted, marketed and commercialised as being more effective for weight loss, and healthier, than weight-reducing diets that have 'balanced' or macronutrient compositions in line with current global dietary recommendations. Healthcare officials argue that very restrictive carbohydrate diets do not promote behaviour changes that foster varied, nutrient- and fibre-rich dietary patterns (USDA 2014), known to reduce risks of cardiovascular disease, hypertension, type 2 diabetes and certain cancers. Extreme restriction or excess of macronutrients, as advised with very low carbohydrate diets, instead promote a way of eating that is likely to result in an imbalance of macronutrient intake, suboptimal micronutrient intake and increased disease risk over time.

Previously, we took stock of existing systematic reviews on low carbohydrate diets for adults wanting to lose weight. We found 50 existing reviews (last search date: 3 March 2014), with a number of shortcomings as reported in Naude 2014. This exercise helped us to identify a gap and inform the protocol for our earlier systematic review and meta-analysis of RCTs (Naude 2014). This Cochrane Review will be a fresh edition to Naude 2014, by taking into account new eligible trials, and comments and criticisms generated by the earlier work.

OBJECTIVES

To compare the effects of low carbohydrate weight-reducing diets to weight-reducing diets with balanced ranges of carbohydrates, in relation to changes in weight and cardiovascular risk, in overweight and obese adults without type 2 diabetes (comparison 1) and with type 2 diabetes (comparison 2).

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-arm individual- and cluster-randomised controlled trials (RCTs) that had an active weight-reducing intervention phase for at least 12 weeks. According to Jensen 2014, obese individuals on a moderately restricted energy intake can potentially lose between six and eight kilograms, or five to ten per cent of initial body weight (clinically meaningful) over a six-month period. From this we surmise that it would be plausible to lose five per cent of initial weight over a three-month period, but not a shorter period. Twelve weeks is, according to the UK National Institute for Health and Care Excellence (NICE), the standard length for most commissioned dietary interventions (Ahern 2017; NICE 2014). Following up participants after the intervention ended can be of any duration.

We will exclude quasi-randomised trials (that is, trials that used an inadequate method of randomisation, such as alternation or date of birth). We will include cross-over trials where the first phase was 12 weeks or longer, and where data for the first phase per group are available. We will exclude cross-over trials that do not meet this criteria due to the possible period and carry-over effects that would arise with the eligible dietary interventions, condition (overweight and obesity) and outcomes in this review, with these not being easily reversible as required for a valid cross-over design (Younge 2015).

We will only include studies with a weight maintenance phase if the preceding weight-reducing phase is for 12 weeks or longer,

and relevant data from this phase are available. We will separate analyses for weight-reducing and weight maintenance phases.

Types of participants

We will include adults (18 years and older) who are overweight or obese (as defined by study authors), with or without type 2 diabetes mellitus, and with or without cardiovascular conditions or risk factors such as hypertension or dyslipidaemia, as defined by trial authors.

We will exclude studies where pregnant and lactating women were included, as well as, studies in people with specific medical conditions such as bipolar disorder, polycystic ovary syndrome, chronic renal disease etc.

We will include studies involving a subset of eligible participants (for example, adults and children, as defined by authors) if results were reported separately for the eligible subset (for example, those ≥ 18 years). If not, we will only include such studies if ≥ 80% of the baseline sample were eligible for our review (for example, aged ≥ 18 years). We will exclude data from such studies in sensitivity analyses to test the robustness of the primary meta-analyses.

Types of interventions

Treatment diet

We will include RCTs investigating low carbohydrate weight-reducing diets where the diets were explicitly implemented for the primary purpose of reducing weight, with or without explicit advice to restrict total energy intake.

Control diet

We will include RCTs where the control adheres to the criteria of weight-reducing diets, with carbohydrate content within the balanced range of 45% to 65% of total energy, where the diets were explicitly implemented for the primary purpose of reducing weight, with or without advice to restrict total energy intake.

We will include studies where diets were implemented by provision of advice, foods or both. However, we will exclude studies with the following:

- Treatment diet has carbohydrate content ≥ 45% of total energy or > 150 g per day.
- Treatment and control diets are different in some other respect that may influence the predefined outcomes, except for total energy intake.
- Treatment or control diets are not adequately defined (and could not be obtained from study authors) or where the control diet is 'no dietary intervention'.
- Diets are combined with any other cointerventions (e.g. exercise, pharmacological, surgical) where these differ by group.
- Dietary interventions have an exclusive focus on energy restriction (i.e. no macronutrient manipulation was explicitly instituted).
- Interventions focus solely on specific foods (e.g. oats), food groups (e.g. dairy) or food components (e.g. plant sterols), or where meal replacements or supplements are part of the diets and are different in the diets being compared.
- Participants are selected based on a possible prognostic variable (for example, genotype).

Types of outcome measures

We will not exclude studies on the basis of outcomes measured. However, we will exclude studies measuring only immediate meal responses (e.g. postprandial changes in blood sugar), and not longer-term physiological responses to diet.

Primary outcomes

- Change in body weight (kg) from baseline
- Number of participants per group with weight loss of at least 5% from baseline

We will assess the primary outcomes at short-term (3 months to < 12 months) and long-term (≥ 12 months) follow-up.

Secondary outcomes

Clinical

- Change in body mass index (BMI; kg/m^2) from baseline
- Number of participants per group with reduction in BMI of at least 5% from baseline

We will assess these clinical outcomes at short-term (3 months to < 12 months) and long-term (≥ 12 months) follow-up.

- Change in diastolic blood pressure (mmHg)
- Change in systolic blood pressure (mmHg)
- All-cause mortality
- Cardiovascular mortality
- Non-fatal myocardial infarction
- Non-fatal stroke
- Diagnosis of type 2 diabetes mellitus (as reported by study authors)

We will assess these clinical outcomes at long-term (≥ 12 months) follow-up.

Laboratory

- Change in glycated haemoglobin (HbA1c) (%)
- Change in serum low-density lipoprotein (LDL) cholesterol (mmol/L)
- Change in serum high-density lipoprotein (HDL) cholesterol (mmol/L)
- Change in serum non-HDL cholesterol (mmol/L)
- Change in serum total cholesterol (mmol/L)
- Change in serum triglycerides (mmol/L)

We will assess these laboratory outcomes at long-term (≥ 12 months) follow-up only.

Adverse effects

Participant-reported adverse effects, specifically with regards to lack of appetite, bad breath, weakness, headaches, gastrointestinal problems (constipation, diarrhoea, flatulence, indigestion) and psychosocial problems (mood disturbances) at any time point, limited to those described in included studies.

Search methods for identification of studies

Electronic searches

We will identify RCTs through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE (PubMed)
- Embase (Ovid)
- Web of Science Core Collection with Indexes = SCI-Expanded, SSCi, CPCI-S (Clarivate Analytics)

We will adapt the preliminary search strategy for MEDLINE (PubMed) for use in the other databases (Appendix 1).

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal for ongoing and unpublished trials (apps.who.int/trialsearch).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status. When necessary, we will seek translations.

Searching other resources

We will check reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We will also examine any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

We will import all deduplicated search records into Covidence (Covidence). Two review authors will independently screen the titles and abstracts of these records to identify all potential eligible studies. Discrepancies in first-line screening choices will be resolved by discussion among at least two review authors. We will retrieve the full-text report for each record that the screeners think is potentially eligible, and two review authors (CN, KN, AS, MS, TY, MR) will independently screen all full-texts, identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (PG or JV). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009). Studies where full reports (published or unpublished) are not available (e.g. conference abstracts), or where there is unclear or missing information (that cannot be obtained from study authors) so that we cannot confirm or refute study eligibility, will be placed with a reason in the 'Studies awaiting classification' table.

Data extraction and management

To extract study characteristics and outcome data, we will create a data collection form in Covidence, and pilot it on at least two included studies. Data from each included study will be extracted independently by two review authors (CN, KN, AS, MS, TY, MR). We will contact the study authors when reported information is unclear or contradictory, or when important data are missing. We will extract information on the following.

- Methods: authors' contact details, type of record (e.g. journal article, thesis), study design, study population, study dates, total duration of the intervention and follow-up duration after the intervention where relevant, details of 'run in' periods where relevant, number of study centres and location, study setting, method of recruitment, number of study arms, description of eligible study arms, outcome used for sample size calculation, unit of allocation, number randomised per study arm (for individually-randomised trials), number of clusters and number of participants per cluster who consented (for cluster-randomised trials), number of withdrawals and those lost to follow-up, number completed and analysed, other relevant notes on the methods.
- Participants: inclusion and exclusion criteria, age, gender (number of males and females per group), baseline body weight status, other baseline cardiovascular disease risk factors and potential confounders, any group differences.
- Interventions: treatment diet, control diet, implementation or delivery of diets, dietary intake assessments (e.g. what, how frequent, by whom), concomitant interventions.
- Outcomes: primary and secondary outcomes specified and collected at relevant time points, data on adherence to the interventions, and whether or not primary study authors analysed results separately according to gender.
- Notes: study funding, conflicts of interest declarations of study authors, and other relevant notes.

For outcomes, we will extract change data (change from baseline to outcome assessment per group) where possible, with relevant data on variance for treatment and control arms and numbers of participants per arm at that time point. Where change data are not available, we will extract and use data at study end (end values), or other relevant time points, along with variance and number of participants per arm at that time point. Where possible, we will convert variables to comparable units to allow pooling of data, if appropriate.

We will measure adherence as the agreement between the prescribed diets and the reported dietary intakes in included studies. We will extract the prescribed and reported total energy intake (kilojoules) at each time point in each group. We will calculate adherence to macronutrients as the difference between the reported and prescribed distributions of energy intake (percentage of total energy) from carbohydrate, fat and protein at the relevant time points, using the Mahalanobis distance equation (Mahalanobis 1936). This equation is useful for measuring the similarity between a set of actual conditions relative to a set of ideal conditions (Rencher 2002). The equation will generate an arbitrary macronutrient adherence score representing the degree of deviation from the prescribed goals for macronutrients in the treatment and control groups, as follows: macronutrient adherence score = √[(mean reported % carbohydrate of total energy - prescribed % carbohydrate of total energy) + (mean reported % fat of total energy - prescribed % fat of total energy) + (mean reported % protein of total energy - prescribed % protein of total energy)].

A lower score indicates better adherence and a higher score, poorer adherence. We will report macronutrient adherence scores

per study per time point by group for energy (kilojoules), total carbohydrate (percentage of total energy), protein (percentage of total energy) and fat (percentage of total energy).

We will resolve disagreements by consensus or by involving a third review author. We will export data from Covidence and import it into the latest version of Review Manager (Review Manager 2014). We will complete the 'Characteristics of included studies' table for all included studies. We will use key items from the TIDieR checklist (Hoffman 2014) to aid description, interpretation and discussion of the results. Brief details of ongoing studies will be reported in the 'Characteristics of ongoing studies' table, and these studies will be considered for inclusion in a future update of the review.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each included study using the Cochrane Risk of Bias 2 tool for randomised controlled trials (RoB 2; Sterne 2019). This tool will assess the effect of the assignment to the intervention, for the following domains:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

Should we encounter cluster-randomised controlled trials, we will assess the following additional domain (Sterne 2019):

- bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomisation.

Should we encounter cross-over trials, we will assess the following additional domains (Higgins 2016):

- period effect;
- carryover effect;
- selective reporting of first period data based on evidence of carry-over (Freeman 1989).

We will judge each domain as either 'low risk of bias', 'some concerns' or 'high risk of bias' for the following outcomes, measured from baseline to ≥ 12 months, which will also be reported in the 'Summary of findings' table for each comparison:

- change in body weight (kg);
- number of participants per group with weight loss of at least 5%;
- cardiovascular mortality;
- change in diastolic blood pressure (mmHg);
- change in HbA1c (%) (for the comparison in diabetic participants);
- change in serum LDL cholesterol (mmol/L);
- participant-reported constipation at any time point.

Overall, per included study, we will make a judgement according to the following criteria:

- low risk of bias: when all domains are at low risk;
- some concerns: when one or more domains have some concerns, but none are at a high risk of bias;
- high risk of bias: when one or more domains are at high risk of bias, or multiple domains have some concerns to the extent that these reduce confidence in the results.

We will resolve any disagreements by discussion or by involving another review author.

Measures of treatment effect

For dichotomous data, we will use the number of events as the numerator and the total sample size per outcome as the denominator in each relevant comparison group and compute the risk ratio (RR) (available case data). For continuous data, we will report results per outcome as the difference in the mean change (and if not available, the difference in end values) between the treatment and control groups, and compute the mean difference (MD) (available case data). We will enter data presented as a scale with a consistent direction of effect. We will use the latest Review Manager version to conduct meta-analyses for each outcome, where appropriate, to determine a pooled effect of low carbohydrate diets compared to balanced carbohydrate diets. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

In the case of multiple intervention groups, we will select one pair of interventions (treatment and control) that is most relevant to this systematic review question. For cluster-randomised trials that did not consider adjustments for clustering, we will reanalyse where possible, following the method of adjusting for clustering, taking into account the correlated nature of within-cluster data, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where a study reports outcome data for more than one time point within our time point categories (3 months to < 12 months; and ≥ 12 months), we will use the longest time point (for example, where results are available at 3 months and 5 months, we will only use the 5 months data).

Dealing with missing data

We will contact study authors or sponsors to clarify key study characteristics and obtain missing numerical outcome data, where needed. Where study authors have not reported all relevant statistics per outcome (for example, sample size, mean change and standard deviation of change per group), we will calculate or estimate the required data from other reported statistics using formulas specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), if possible. If we cannot calculate or estimate these statistics with reasonable confidence, we will contact the authors by email. Where we do not receive a response we will not impute the missing values but will report the available results narratively or in a table, as appropriate. For interventions in which there is substantial attrition (15% or more for at least one of the groups) of study participants, we will report the attrition rate and perform sensitivity analyses excluding these studies.

Assessment of heterogeneity

We will examine heterogeneity per outcome firstly by visual inspection of the forest plots (i.e. we will look at physical overlap of confidence intervals across the included studies). Secondly, we will assess statistical heterogeneity among the intervention effects across the included studies in each meta-analysis as follows.

- Chi^2 test for heterogeneity.
- I^2 statistic to quantify heterogeneity.
- Tau^2 statistic to measure the extent of heterogeneity.

In our meta-analyses we will consider substantial heterogeneity as an I^2 value of greater than 50% and either a Chi^2 of less than 0.1 or Tau^2 greater than 0. In meta-analyses where we find substantial heterogeneity, we will perform prespecified subgroup analyses on outcomes in the 'Summary of findings' tables, as data allows. Where we identify unexplained substantial heterogeneity, we will not pool results into an overall effect estimate but rather present the individual effect sizes per study for the specific outcome.

Assessment of reporting biases

If data per comparison and outcome allow us to pool more than 10 studies, we will with a funnel plot explore the possibility of small study biases for the primary outcomes. In the case of asymmetry, we will consider various explanations such as publication bias, poor study design and the effect of study size.

Data synthesis

We will use a random-effects model for meta-analyses since we anticipate heterogeneity between included studies due to variations in the composition of weight loss diets, adherence to diets, intervention duration and dietary assessment methodology. For dichotomous outcomes, we plan to use the Mantel-Haenszel method, unless the number of events are not available but estimates of effect measure and its standard error are, in which case we will use the inverse variance method. For continuous outcomes, we will use the inverse variance method.

We will analyse trials in overweight and obese participants without (comparison 1) and with type 2 diabetes (comparison 2) separately where possible as the presence of diabetes is likely to influence the effects of the diets.

We will assess the comparability between individually-randomised trials and cluster-randomised trials with sensitivity analyses, where data allow by first pooling cluster- and individually-randomised trials and then pooling only studies that randomised individual participants.

We will analyse outcome data at the time point ≥ 12 months, because it captures sustainability of effects on weight loss, clinical as well as laboratory outcomes. However, for the weight and BMI outcomes, we will also analyse data at the time point 3 months to < 12 months, as many people going on diets are especially interested to know how fast they would be losing weight.

We will preferentially extract and use data from trials' intention-to-treat (ITT) analyses (as reported by trial authors) in all our meta-analyses. By ITT, we mean that participants who were randomised were analysed according to the group to which they were randomised; however, if there are missing data we will not perform any imputations.

'Summary of findings' table

Based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we will prepare two 'Summary of findings' tables, one for each comparison. We will include the following outcomes measured from baseline to ≥ 12 months in these tables: change in body weight (kg); number of participants per group with weight loss of at least 5%; cardiovascular mortality; change in diastolic blood pressure (mmHg); change in HbA1c (%) (for the comparison in diabetic participants); change in serum LDL cholesterol (mmol/L); as well as participant-reported constipation at any time point. We will use the GRADE system to rank the certainty of the evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes, using GRADEprofiler (GRADEpro) software (www.gradepro.org). The GRADE tool includes five considerations (study limitations, inconsistencies of results, imprecision, indirectness and publication bias) to assess the certainty of the evidence.

We will justify all decisions to downgrade the quality of evidence using footnotes, and we will make comments to aid readers' understanding where necessary.

Two review authors (from CN, AS, KN) will make judgements about evidence certainty, with disagreements resolved by discussion, and involving a third review author where needed.

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review. An example of a 'Summary of findings' table is included as Table 1.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses for the primary outcomes, to explore the stability of findings in different study subgroups, as follows.

- By extent of carbohydrate restriction (i.e. very low carbohydrate or ketogenic diets: carbohydrate prescription of ≤ 50 g per day or < 10% of total daily energy intake from a nominal 8400 kilojoule (approximately 2000 kcal) diet; and non-ketogenic low carbohydrate diets: > 50 g to 150 g per day or < 45% of total energy intake).
- By similarity of total energy prescription (i.e. studies with substantial differences in daily total energy prescription (> 500 kilojoules) in treatment and control groups, studies with similar energy intake prescribed in treatment and control groups, studies with unknown and unrestricted energy intake prescribed in treatment and control groups).
- By diagnosed cardiovascular event or disease (i.e. studies in people with no events or disease, studies in people with events or disease, and studies in people with and without events or disease).
- By gender.

Sensitivity analysis

We plan to carry out sensitivity analyses for primary outcomes, assessing the effect of:

- overall low risk and 'some concerns' of bias (i.e. first pool all relevant studies per outcome, and then pool only studies with overall low risk and 'some concerns' of bias);
- attrition bias (i.e. first pool all relevant studies per outcome, and then pool only studies with < 15% missing data from the total initial sample);

- studies including only a subset of eligible participants for this review (i.e. first pool all relevant studies per outcome, and then pool only studies that included only participants eligible for inclusion in this review); and
- clustering (i.e. first pool all relevant studies per outcome, and then pool only studies that randomised individual participants); and
- source of funding (i.e. first pool studies with all funding sources, and then pool only studies without diet/food industry funding).

Summary of findings and assessment of the certainty of the evidence

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ADDITIONAL TABLES

Table 1. Example 'Summary of findings' table

Low carbohydrate versus balanced carbohydrate weight-reducing diets for 12 months or longer in overweight and obese adults with type 2 diabetes

Participants or population: overweight and obese adults with type 2 diabetes
Settings: primary care
Intervention: low carbohydrate weight-reducing diets
Comparison: balanced carbohydrate weight-reducing diets

Follow-up: ≥ 12 months

Outcomes	Balanced diets	Low carbohydrate diets	Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
	Illustrative range of change in average values from pre-diet levels by study: range across studies[a]	*The effect difference with low carbohydrate diets in randomised comparison to diets with balanced carbohydrate (95% CI)*			
Change in body weight (kg)	From [value] lower to [value] kg higher	[value] kg lower weight		[value]	⊕⊖⊖⊖ **very low**

Table 1. Example 'Summary of findings' table *(Continued)*

		(could be [value] lower to [value] higher)		([value] studies)	⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Number of participants per group with weight loss of at least 5%	[number] per 1000 participants	[number] per 1000 participants (range)	RR (95% CI)	[value] ([value] studies)	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Number of participants per group who died due to cardiovascular diseases	[number] per 1000 participants	[number] per 1000 participants (range)	RR (95% CI)	[value] ([value] studies)	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Change in diastolic blood pressure (mmHg)	From [value] lower to [value] mmHg higher	[value] mmHg lower diastolic blood pressure (could be [value] lower to [value] higher)		[value] ([value] studies)	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Change in HbA1c (%)	From [value] lower to [value] % higher	[value] % lower HbA1c (could be [value] lower to [value] higher)		[value] ([value] studies)	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Change in serum LDL cholesterol (mmol/L)	From [value] lower to [value] mmol/L higher	[value] mmol/L lower LDL cholesterol (could be [value] lower to [value] higher)		[value] ([value] studies)	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low**

Table 1. Example 'Summary of findings' table *(Continued)*

				⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Participant-reported constipation	[number] per 1000 participants or From [value] lower to [value] higher as relevant	[number] per 1000 participants (range) or [value] lower (could be [value] lower to [value] higher) as relevant	[value] ([value] studies)	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**

CI: confidence interval; **HbA1c**: glycated haemoglobin; [a]Note this is the univariate average change observed between follow-up and baseline in the control group

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.

APPENDICES

Appendix 1. Preliminary MEDLINE (PubMed) search strategy

#1 Search **randomized controlled trial [pt]**

#2 Search **controlled clinical trial [pt]**

#3 Search **randomized [tiab]**

#4 Search **placebo [tiab]**

#5 Search **clinical trials as topic [mesh: noexp]**

#6 Search **randomly [tiab]**

#7 Search **trial [ti]**

#8 Search **(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)**

#9 Search **(animals [mh] NOT humans [mh])**

#10 Search **(#8 NOT #9)**

#11 Search **("low carbohydrate" OR "lower carbohydrate" OR "high fat" OR "higher fat" OR "high protein" OR "higher protein")**

#12 Search **"ketogenic diet"**

#13 Search **("carbohydrate restricted" OR "carbohydrates restricted" OR "fat restricted" OR "protein restricted")**

#14 Search **("low carbohydrates" OR "lower carbohydrates")**

#15 Search **("balanced diet" OR "recommended diet")**

#16 Search **("reduced carbohydrate" OR "reduced carbohydrates" OR "reduced fat" OR "reduced protein")**

#17 Search **("macronutrient manipulation" OR "macro nutrient manipulation" OR "macronutrients manipulation" OR "macro nutrients manipulation")**

#18 Search **"ketogenic diets"**

#19 Search **(#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)**

#20 Search **"Diet, Carbohydrate-Restricted"[Mesh]**

#21 Search **"Diet, High-Fat"[Mesh]**

#22 Search **"Diet, High-Protein Low-Carbohydrate"[Mesh]**

#23 Search **"Diet, High-Protein"[Mesh]**

#24 Search **"Diet, Ketogenic"[Mesh]**

#25 Search **"Diet, Fat-Restricted"[Mesh]**

#26 Search **"Diet, Mediterranean"[Mesh]**

#27 Search **(#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)**

#28 Search **(#19 OR #27)**

#29 Search **("weight reducing diet" OR "weight reducing diets" OR "weight loss diet" OR "weight loss diets" OR "calorie restricted diet" OR "calorie restricted diets" OR "energy restricted diet" OR "energy restricted diets" OR "kilojoule restricted diet" OR "kilojoule restricted diets")**

#30 Search **("isocaloric diet" OR "hypocaloric diet" OR "isoenergetic diet" OR "hypoenergetic diet")**

#31 Search **("isocaloric diets" OR "hypocaloric diets" OR "isoenergetic diets" OR "hypoenergetic diets")**

#32 Search **("iso caloric diet" OR "hypo caloric diet" OR "iso energetic diet" OR "hypo energetic diet")**

#33 Search **("iso caloric diets" OR "hypo caloric diets" OR "iso energetic diets" OR "hypo energetic diets")**

#34 Search **"Diet, Reducing"[Mesh]**

#35 Search **"Caloric Restriction"[Mesh]**

#36 Search **(#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)**

#37 Search **(#10 AND #28 AND #36)**

WHAT'S NEW

Date	Event	Description
10 December 2019	Amended	Description of Risk of Bias 2.0 included to replace description of Risk of Bias 1.0

CONTRIBUTIONS OF AUTHORS

CN drafted the protocol and AS, KN, MS, TY, MR, PG and JV provided inputs to finalise this protocol.

DECLARATIONS OF INTEREST

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KN: none known

MS: none known

PG: is the Director of READ-It, funded by UK Aid, an Initiative that aims to increase the number of evidence-informed decisions in LMICS by global, regional and national decision makers that benefit the poor and vulnerable, including women

MR: none known

JV: none known

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Internal sources

- No sources of support supplied

External sources

- READ-It, UK.

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