Low-carbohydrate diets for overweight and obesity: A systematic review of the systematic reviews

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Abstract

Low-carbohydrate diets are being widely recommended, but with apparently conflicting evidence. We have conducted a formal systematic review of the published systematic reviews of RCTs between low-carbohydrate vs. control (low-fat/energy-restricted) diets in adults with overweight and obesity. In MEDLINE, Embase, Web of Knowledge and Cochrane Database of Systematic Reviews, searched from inception to September 2017, we identified 12 systematic reviews, 10 with meta-analyses. Differences in methods, study-quality, weight-change, and citations of published systematic reviews were assessed by AMSTAR-2. Review methods varied in definitions of low-carbohydrate, databases searched, and bias assessment. Overall review quality was high in two, moderate in three, critically low in seven. Among meta-analyses, 4/5 with critically low quality showed low-carbohydrate diet superiority for weight loss (0.7-4.0 kg), while high quality meta-analyses reported little or no difference between diets. Greater numbers of participants correlated with smaller differences in weight loss ($r=0.73$, $p=0.03$). More citations correlated with lower review quality ($rho= -0.9$, $p=0.037$), with larger differences in weight loss ($rho= -0.9$, $p=0.037$), and with journal impact factor ($rho=1.0$, $p=0.01$). In conclusion, publication acceptance and citations appear to favour apparently larger effect-sizes above methodological quality. Better quality reviews and RCTs are needed, before recommending low-carbohydrate diets as preferred to other approaches for energy restriction.

Abbreviations

LCD, low-carbohydrate diet

RCT, randomised controlled trial

LFD, low-fat diet

TG, triglyceride

LDL, low-density lipoprotein cholesterol

CHO, carbohydrate

PRISMA, Preferred Reporting Items of Systematic reviews and Meta-analyses

CDSR, Cochrane Database of Systematic Reviews

BMI, body mass index

TC, total cholesterol

HDL, high-density lipoprotein cholesterol

AMSTAR, A MeaSurement Tool to Assess systematic Reviews

RoB, risk of bias

T2DM, diabetes mellitus type 2

LEARN, Lifestyle, Exercise, Attitudes, Relationships, and Nutrition

VLCKD, very low-carbohydrate ketogenic diet

Introduction

Low-carbohydrate diets (LCD) have been increasingly used for weight reduction in recent years and been heavily promoted in the media and scientific publications (1-3). Public interest in LCD might be traced to a letter by William Banting published in 1863, describing his own successful weight loss by limiting carbohydrates (CHO) intake (4). It has become popular again recently with a plethora of best-selling books providing a weight loss diet by eliminating bread, pasta, grains, fruits, starchy vegetables, and liberal consumption of animal protein, fat, cheese, cream and butter (5). Evidence for their effectiveness, and whether there is any specific effect other than through energy restriction, has however been hotly debated.

Many randomised controlled trials (RCT) have been conducted, with conflicting results. A series of systematic reviews and meta-analyses have been conducted to investigate RCT methodologies, and to try to establish the effectiveness of LCDs compared to low-fat diets (LFD) or energy-restricted weight loss diets (6-11). However, they too have drawn inconsistent conclusions. For example, Mansoor et al. (12) showed a greater reduction in body weight and triglyceride (TG) in subjects following LCDs compared to LFDs while an apparently similar meta-analysis reported no difference in weight loss but a rise, or no reduction, in low-density lipoprotein (LDL) cholesterol (13). Differences in inclusion and exclusion criteria, or biases inherent in the designs of included trials, might contribute to disagreement among published meta-analyses. Even the definition of an LCD used may vary, as it can encompass a range of CHO intake from 20 to 120 g/day, or 20% to 45% energy from CHO (12-14).

Systematic reviews and meta-analyses are regarded as the final scientific arbiter, essential for synthesis of scientific evidence, using comprehensive and reproducible approaches along with methodological assessments of the included studies (15). A survey in PUBMED showed a rapid increase in publication of systematic reviews and meta-analyses from 1991-2014, more than

half of them might be flawed, misleading and unnecessary (16). These factors have accelerated an additional design of evidence synthesis - overview of systematic reviews or systematic review of systematic reviews, which systematically identify and critically appraise multiple systematic reviews and meta-analyses in a single document, aiding clinical decision making and guideline development (17).

One of the benefits and purposes of this approach is to compare methods used and assess the quality of the included systematic reviews, which could explore the inconsistency of their results (17, 18), as in the meta-analyses of effects of LCDs. It is clearly important to eliminate bias in conducting and reporting of intervention studies. However, quality assessment of the systematic review process, itself potentially open to bias, is also important for evaluating the reliability of conclusion, and may be neglected when systematic reviews are cited.

Objectives of the present study were: 1) to document differences in the methods, study-quality and conclusions of published systematic reviews with meta-analyses; and 2) to evaluate the weight loss outcomes reported in meta-analyses, in relation to the quality of published systematic reviews.

Methods

Protocol and registration

The present systematic review of systematic reviews was conducted using the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) statement (19). A systematic review protocol was registered at the PROSPERO with the registration number CRD42018072137 (20).

Eligibility criteria

Papers were eligible if they met the following criteria:

i. Systematic reviews, with and without meta-analyses, of randomised controlled trials.
ii. Compared any types of LCDs to control diets (LFDs or energy-restricted diets); papers were excluded if the intervention included additional components such as exercise or drugs.
iii. Involved subjects of either sex, with baseline body mass index (BMI) ≥25 kg/m^2: papers were excluded if the study population included subjects whose BMI less than 25 kg/m^2.
iv. Meta-analyses reported mean differences in weight loss as the primary outcome between the two diets, at any length of follow-up.
v. Limited to English language
vi. Publication after 2000 until September 2017

The present systematic review thus included systematic reviews involving a variety of LCDs such as Atkins Diet, Paleolithic diet, Zone Diet, Sugar Busters, Harcombe, ketogenic diet, very low CHO diet, or as stated as included by the authors of each systematic review.

The primary outcome for the present systematic review was mean differences in weight loss reported in meta-analyses between LCDs and the control (LFDs or energy-restricted) diets.

Secondary outcomes were lipid profile, fasting blood glucose and insulin, blood pressure, glucose tolerance test, adverse effects, and the publication and citation metrics of the papers included.

Search and Information sources

We conducted a systematic literature search in electronic databases including MEDLINE (OvidSP), Embase (OvidSP), Web of Knowledge and Cochrane Database of Systematic Reviews (CDSR). Published conference abstracts and reference lists of included reviews were also searched. In order to explore the effects of LCDs on weight loss, the following free-texts and MeSH terms were used: low-carbohydrate diet; restricted carbohydrate; very low carbohydrate diet; ketogenic diet; Atkins Diet; Paleolithic diet; Zone diet; Sugar Busters diet; South Beach diet; Harcombe diet; weight loss; weight reduction; low fat diet; overweight; obesity; systematic review; review; and meta-analysis. The full search strategy for MEDLINE is available as online supporting information (Table S1).

Study selection

All identified records from each database were exported to Endnote (Endnote X8, Thomson Reuters, New York, USA). Duplicates were excluded. Two authors (CC and MK) independently screened and excluded irrelevant titles and abstracts. The remaining potential eligible records, including those with disagreement at this step, were then included for full-text screening against eligibility criteria. A third author (EC) was consulted over nine cases when there was disagreement at the full-text level between the two reviewers, primarily about whether the dietary interventions in individual RCTs should be considered LCDs.

Data extraction

A data extraction template was created using Microsoft Excel. Two authors (CC and MK) performed data extraction independently. Disagreements were resolved by consensus or consulting a third author (EC) where there was an issue related to data extraction. The following information was extracted:

1) Systematic review information (e.g. author name, title, year)
2) Methods of each systematic review (e.g. protocol registration, objective, search strategy and databases, inclusion and exclusion criteria, definitions of LCDs and LFDs)
3) Numbers of included trials and numbers of total participants from each review.
4) Numerical outcomes of weight loss, TG, LDL, high-density lipoprotein cholesterol (HDL), total cholesterol (TC), glucose, insulin, and blood pressure. All measurement units were converted to the SI unit.
5) Numbers of citations in SCOPUS and in Google Scholar, 3 years after publication.
6) Funding sources for each review and potential conflict of interest of review authors.

Quality assessment

Two authors independently performed quality assessment of included reviews using 'A MeaSurement Tool to Assess systematic Reviews 2' (AMSTAR 2), disagreements were solved by consensus or consulting the third author (21). As suggested by Shea et al., critical domains or items of the tool were identified, for evaluating and classifying the included studies, as well as total score (21). Critical domains where errors or biases would seriously affect the validity of conclusions of the included reviews were identified as following (Item 4, 9, 11-15; Table 1):

i. Items relating to comprehensive literature searching,
ii. Statistical analysis of combined result including investigating causes of heterogeneity,
iii. Methods of the risk of bias (RoB) assessment,
iv. The impact of RoB on pooled results, discussion and conclusion,
v. Assessment of publication bias.

We rated the overall quality of the included reviews as following (Table 1):

- ‘high’ methodological quality if the included reviews did not contain any of critical domains but could have up to 3 non-critical domains;
- ‘moderate’ if had more than 3 non-critical domains;
- low if had one critical domain; and
- ‘critically low’ if had more than one critical domains.

A total quality score was also applied to each review. One point for each AMSTAR item was given if included review met the answer ‘Yes’, 0.5 point for ‘Partial Yes’, and no point for ‘No’. A full total score of 13 is for systematic reviews without meta-analysis, and of 16 for systematic reviews with meta-analyses.

Data synthesis

A narrative synthesis was used to describe reviews’ characteristics, method, quality and their conclusions. Because the meta-analytic technique is to increase statistical power by increasing sample size, published meta-analyses with fewer studies and small sample size could influence the magnitude of effect size (15). Therefore, correlations between ‘weight loss effect size’ and numbers of primary studies, and numbers of subjects (from each meta-analysis) were investigated using Pearson’s correlation coefficient after scatter plot suggesting of potential linear relationship pattern. In addition, a correlation between ‘weight loss effect size’ and quality score was analysed by Spearman’s rank correlation. Spearman’s rank correlation coefficient was also used to investigate whether the popularity (citation count) of published meta-analyses is related to the highest quality of the meta-analysis, to the ‘weight loss effect size’, or the reputation (impact factor) of the journal.

Results

Identification of systematic reviews

We retrieved 235 records from literature searching. After duplicates were removed, 201 titles and abstracts were screened for inclusion, resulting in 39 full-text articles to be assessed for eligibility. Excluded full-texts with reasons are presented in Table S2. A total of 12 systematic reviews, 2 without meta-analysis (22, 23) and 10 with meta-analyses (10, 12-14, 24-29), were included for data synthesis and quality assessment (Figure 1).

Systematic reviews without meta-analyses: methods, quality and outcomes

The characteristics of the two systematic reviews without meta-analysis are summarised in Table 2 and 3. All of them included primary studies with LCDs in participants with overweight and obesity, one reported weight loss and HbA1c outcomes (22) while the other reported only weight loss outcome (23). None of them reported adverse effects. Both systematic reviews did not report information about their written protocols, performing study selection and data extraction in duplicates, and RoB assessment, resulting in a judgement of critically low quality for these two reviews, Table 6.

A systematic review by Castaneda-Gonzalez et al. (22) aimed to evaluate effects of LCDs on weight loss and glycaemic control in participants with type 2 diabetes mellitus (T2DM), compared to various controls including LFDs, usual care diets, or low glycaemic diet. The review authors defined LCD as maximum intake of CHO less than 130 g/day and included only RCTs as study design. Eight studies were included for this systematic review, but one of them was not an RCT (30). This review also reported an incorrect amount of CHO intake of one RCT (31). Among eight included studies, five reported weight loss outcomes. Three studies, of 3-4 months, found significantly greater weight loss with LCDs (3.1 to 11.1 kg from baseline) compared to control diets (0.8 to 6.9 kg from baseline). In contrast, two studies with longer

duration (1-2 years) found no significant differences in weight loss between the two diets (LCDs, 3.1 to 3.8 kg vs. LFDs, 3.1 to 3.2 kg, from baseline). Regarding HbA1c, LCDs decreased HbA1c by 0.02 to 1.5% as did LFD by 0 to 0.5%, however, these effects were inconsistent. Only 2 out of 6 RCTs showed significantly greater reductions in HbA1c following LCDs compared to LFDs (22).

The other systematic review without meta-analysis, by Dutton et al. (23), evaluated the effects on weight loss of diet composition, use of food provision and modality of treatment delivery. Only PubMed was searched. Among included studies, 10 RCTs of LCD interventions compared to various types of control diets (e.g. LFD, Mediterranean diet, or commercial diets: LEARN, Ornish, Zone diet), but the LCD was not defined in the inclusion criteria. Participants of included RCTs had BMI greater than 25 kg/m^2 with and without co-morbidities. Duration of intervention ranged from 2 to 12 months with follow-up periods up to 48 months. The authors concluded that LCDs might result in greater weight reduction over LFDs for a short period, but this was not consistent among studies. Most studies failed to show benefit for one diet or the other over a longer follow-up (23).

Systematic reviews with meta-analyses

The characteristics of the ten meta-analyses are summarised in Table 4 and 5. All aimed to evaluate the effectiveness of LCDs compared to LFDs on weight reduction and metabolic parameters. One meta-analysis by Johnston et al. used a network meta-analysis for pooled results (29).

Participants

All meta-analyses included RCTs among participants with overweight and obesity, with and without co-morbidities that included type 2 diabetes, hypertension, dyslipidaemia, cancer,

polycystic ovarian syndrome, and others. One meta-analysis included RCTs conducted solely among self-reported 'healthy' participants (12). The meta-analysis by Naude et al. (13) performed an analysis between participants with and without diabetes separately. (Table 4)

Interventions

The definition of LCD varied among meta-analyses: four included LCD with CHO <60g/day or <20% energy per day, while another five included LCD with CHO <120 g/day or up to 45% energy per day. One meta-analysis did not define LCD other than as declared by the RCTs' authors (26). Among these meta-analyses, one focused solely on commercial weight loss diets, which included Atkins, Zone, South Beach, Ornish, Rosemary and LEARN diets (29); and another one used the term 'very low carbohydrate ketogenic diet' (VLCKD) which included CHO less than 50 g/day (25). Nine meta-analyses used LFDs as comparators, which comprised of less than 30% energy contribution from fat. Another one (13) used isocaloric balanced weight loss diet (CHO:Fat:Protein; 45-65:25-35:10-20% of energy) as a comparator to LCD, which explored the effectiveness of LCD on weight reduction when the energy intake was equal to that of a 'balanced' weight loss diet. (Table 4)

Search methods of included meta-analyses

MEDLINE was the most searched database (n=10), followed by EMBASE (n=7) and CDSR (n=4). Five meta-analyses searched trial registries (e.g. Clinicaltrials.gov; The Cochrane Central Register of Controlled Trials, CENTRAL). Two meta-analyses searched only one database (14, 24). Numbers of included RCTs from each meta-analysis ranged from 5 to 48 RCTs comprising of 447 to 7286 participants. (Table 5)

Methodological quality of included meta-analyses

Methodological quality assessment is presented in Table 6. According to AMSTAR 2 items described in the method section, all published meta-analyses described their research question or objectives following the PICO (Item 1). Most of the included meta-analyses conducted a comprehensive literature search, and performed study selection and data extraction in duplicate (Item 3-6). The AMSTAR 2 items that most of the meta-analyses failed to meet were the following: protocol registration (Item 2); provide a list of excluded RCTs with justification (Item 7); and report on the source of funding for the included RCTs (Item 10).

Critical Domains: Four meta-analyses assessed the RoB using the Cochrane Collaboration Risk of Bias Tool, three assessed only some items of this tool, while the rest of the meta-analyses did not report RoB assessment. Six meta-analyses assessed or discussed the impact of RoB on pooled results. Four meta-analyses did not plan to investigate the causes of heterogeneity resulting in the answer 'No' for item 11 – appropriate methods for statistical combination of results; and item 14 – explain/discus heterogeneity observed in the results of the review. Eight out of ten meta-analyses investigated the publication bias.

Overall quality rating: Methodological quality of included meta-analyses was classified by the AMSTAR 2 method as 'critically low' for five out of ten meta-analyses (14, 24, 26-28), 'moderate' for three (10, 12, 29) and 'high' for two meta-analyses (13, 25). (Table 4)

Reported risk of bias of primary RCTs

Of four meta-analyses that assessed all items of the RoB tool, allocation concealment and blinding outcome assessment were judged as unclear to high RoB. Incomplete outcome data were also judged as high RoB across the included RCTs.

Attrition rates and adherence

Attrition rates were high, and varied across the RCTs. Attrition rates in LCD groups ranged from apparently zero to 60% of participants as did as control diets from 0 to 54%. A meta-analysis by Naude et al. (13) calculated adherence scores for macronutrient goals in LCD and an isocaloric balanced weight loss diet. The scores varied among primary RCTs. At 3-6 months, of 13 RCTs, 4 showed similar adherence to prescribed macronutrient goals in the two diets, 5 showed better adherence scored with LCD and 4 showed better adherence with a balance weight loss diet. In contrast, at 12 months, 3 RCTs showed better adherence with LCD while 5 RCTs showed better adherence with a balanced weight loss diet intervention (13).

Publication bias, funding sources of meta-analyses and authors' conflict of interests

Only eight meta-analyses assessed the publication bias using funnel plot or statistical test. Weight loss outcome was subject to publication bias in seven out of 8 meta-analyses, Table 5. Four meta-analyses (three of critically low; one of moderate quality) and/or their authors were supported by commercial organisations, as well their pooled results showed a superiority of LCDs over LFDs. Another four meta-analyses (one of critically low; two of moderate; one of high quality) were supported by non-commercial organisations such as university or research institutes, while the rest reported no funding or no conflict of interest. (Table 5 and 7)

Effect of intervention on weight reduction

Five meta-analyses synthesised pooled effects at 6 and 12 months, one at 12 months, and four synthesised their results regardless of the duration of intervention (2-24 months). At 6 months, evidence from a high methodological quality meta-analysis by Naude et al. (13), comparing LCDs (<45%E from CHO) with isocaloric balanced diets, demonstrated no difference in weight loss outcome between the two diets. Two moderate quality meta-analyses showed contrary results as following: a network meta-analysis (<40%E CHO) by Johnston et al. (29) reported no difference in weight loss while another meta-analysis by Nordmann et al. (10) reported a

significantly greater weight change of -3.3 kg following LCD (<60g CHO) compared to LFD (mean weight change following LCD minus LFD, negative value indicates subjects lost more weight following LCD than those who followed LFD; I^2=65%, p=0.02). Two critically low quality meta-analyses (24, 27) reported a significantly greater weight change following LCD compared to LFD from -1.4 to -4.0 kg with significantly high heterogeneities (I^2=65-91%).

At 12 months, three out of six meta-analyses (two of critically low; one of high quality) reported a greater weight change in LCD, by -0.77 to -1.0 kg compared to LFD (I^2=0-48%). Generally, meta-analyses with significant results favouring LCDs included RCTs with CHO <60g/day, whereas three out of five meta-analyses with CHO contributing toward up to 45% energy showed no difference in weight loss between the two diets. (Table 7)

Serum Triglyceride and cholesterol

Seven meta-analyses reported mean differences in TG, LDL and HDL-cholesterol outcomes, and six for TC outcome, Table S3-S6. None of them reported whether the differences in these outcomes, in their included RCTs, were adjusted to weight loss. A high quality meta-analysis by Naude et al. of LCD vs. isocaloric balanced diet reported no difference in mean reduction in TG and TC between the two diets. A subgroup analysis, however, showed that participants without diabetes assigned to LCD had increased LDL-cholesterol at 6 months greater than LFD (0.09 mmol/l; 95%CI 0.0 to 0.18; I^2=32%, p=0.14; 12 trials), and had increased HDL-cholesterol at 12 months (0.04 mmol/l; 95%CI 0.01 to 0.08; I^2=35%, p=0.16) (13).

In contrast, another high quality meta-analysis by Bueno et al. demonstrated a greater reduction in TG level following VLCKD than LFD (-0.18 mmol/l; 95%CI -0.27 to -0.08; I^2=12%, p=0.33; 12 trials), but a significant rise in LDL-cholesterol (0.12 mmol/l; 95%CI 0.04 to 0.20; I^2=0%, p=0.70) (25). Consistent findings of decreased TG but increased LDL-cholesterol following LCDs were

also reported across the remaining meta-analyses, regardless of duration and amount of CHO intake. Mean difference in changes in HDL-cholesterol between LCDs and LFDs increased in 5 out of 7 meta-analyses by 0.04-0.14 mmol/l (I^2=0-78%) while TC showed inconsistent results.

Glucose, insulin, HbA1c and blood pressure

There was no difference in reduction in glucose (5 meta-analyses), insulin (3 meta-analyses) and HbA1c (2 meta-analyses) between the two diets, Table S7-S9. No meta-analyses reported whether the differences in these outcomes were adjusted to weight loss. Seven meta-analyses reported mean differences in SBP, and six meta-analyses for DBP, Table S10-S11. No significant differences in effects on systolic and diastolic blood pressure were reported at 6 months. At 12 months, one meta-analysis, of critically low quality (27), LCDs showed a greater reduction in SBP by 2.19 mmHg (95%CI -4.35 to -0.03; I^2=28%, p=0.23). In addition, another one meta-analysis, of high quality (25), demonstrated a greater reduction in DBP by 1.43 mmHg (95%CI -2.49 to -0.37; I^2=3%, p=0.41) following VLCKD compared to LFDs.

Adverse effects

Only one meta-analysis, of moderate quality, reported adverse effects of LCDs, including constipation, headache, halitosis, muscle cramp and general weakness (29).

Correlations between weight loss effect size, quality score, number of studies and number of subjects

Network meta-analysis (29) was excluded from this analysis, as there was no direct comparison of interventions. Nine meta-analyses were analysed for correlation. Mean differences in weight loss between LCD vs. LFD were positively correlated with quality score, number of primary studies and number of participants in each meta-analysis, (Table 9). Among these meta-analyses, greater numbers of participants were significantly correlated with smaller mean

differences between the two diets (r=0.73, p=0.03), suggesting that bigger reported differences were more likely to be chance findings.

Correlations between citation number, weight loss effect size, quality, and impact factor.

Citation numbers of each meta-analysis from Scopus and Google Scholar are demonstrated in Table 10. Only five meta-analyses had citations up to 3 years. Correlation analysis showed that a higher number of citations of a meta-analysis was correlated with a lower quality score (lower ranking methodological quality; rho= -0.9, p=0.037); and citation number was associated with larger mean differences in weight loss between LCD and LFD (rho= -0.9, p=0.037). Undoubtedly, citation number was strongly correlated with the impact factor of the journal (rho= 1.0, p=0.01). These analyses suggest that acceptance of a meta-analysis by a major (high impact factor) journal, and subsequent citation, are more influenced by the apparent effect size reported than by the quality of the research.

Discussion

At their inception, a systematic review was considered an almost infallible route to definitive knowledge, based only on well-designed scientific research with little or no RoB or error. However, it is clear that well-conducted systematic reviews can in fact draw differing conclusions for the same research questions. The present paper has attempted to conduct a systematic review and quality assessment of existing systematic reviews of the published evidence, on a topic of enormous scientific debate and public interest. It explores the differences between the conclusions of existing systematic reviews, and the factors which might contribute to biasing systematic reviews one way or the other.

Published systematic reviews have a substantial variation in their methods, which included the definition of LCD, number of databases searched, RoB assessment, and investigation of causes of heterogeneity. This variation contributed to differences in methodological quality and their synthesised results. Most meta-analyses are of rather low methodological quality regarding critical domains of AMSTAR 2 tool: lack of assessment of the RoB and impact of RoB on the pooled results, and lack of appraisal of the drivers of heterogeneity.

Adopting LCD involves excluding usual high-CHO foods, thus inevitably reducing energy intake, but without specifically counting or restricting energy intake. Definition of LCD remains an issue when communicating the effects of LCD. The cut-off ranges from <60g/day to <45%E as the latter cut-off may regard to dietary guidelines that recommend CHO intake for 45-65% of daily energy intake. Meta-analyses with more extreme CHO restriction (<60g/day), and shorter duration (6 months follow-up) reported significantly greater weight loss than LFD/energy-restricted control diets. The weight loss effect attenuated when the amount of CHO increased or the longer follow-up. This could be from losing adherence to the prescribed diet, in both groups of intervention. Losing adherence to diets or high attrition rate are major problems in all nutrition

research among free-living subjects (32, 33). Combining behavioural therapy and frequent follow-up could help increase adherence and lower attrition rate (32, 34).

Critically low quality meta-analyses showed a superiority of LCD for weight loss while moderate quality showed inconsistent results, and high quality showed little or no difference. This is also demonstrated by the association between a high quality ranking and a limited mean difference in weight loss between LCD vs. LFD. In addition, nine out of ten meta-analyses' results were subject to publication bias favouring the LCD, which might be from the inclusion of RCTs with small sample size and positive results tend to be published (35). However, we found that higher numbers of participants were significantly correlated with lower mean differences in weight loss between LCD vs. LFD. This does not mean that there is no publication bias in meta-analyses with larger sample size, but it could be because these meta-analyses with larger sample size included larger RCTs with lower risk of small-study errors, leading to less bias in the meta-analysis results (36).

A high quality meta-analysis of VLCKD vs. LFD reported a greater weight loss with VLCKD of 0.9 kg at 12 months (25). This difference, however, is small and may not infer clinical significance favouring LCD over LFD. Differences up to about 2kg in body weight could be a result of depleted glycogen storage with LCD rather than body-fat loss, an effect which may develop at 12-months after 2-3 days re-adherence to LCD (37). Notably, another high quality meta-analysis reported no difference in weight loss between LCD and isocaloric balanced weight loss diet when the energy intakes of the two diets were equally prescribed (13). Similar findings from two large RCTs with 811 and 609 participants, followed up for 1-2 years, confirmed that reduced energy intake, with varying macronutrient composition, produced similar weight loss (38, 39). This supports the basic Newtonian principle of energy balance; weight loss

occurs when energy intake is less than energy expenditure regardless of macronutrient composition of the diets (40).

Together, it appears that LCDs are as effective as low-fat diets for inducing weight reduction. Both diets, applied in free-living subjects, can reduce body weight by approximately 3 to 10 kilograms below baseline (11, 13, 38). This amount of weight loss often has some clinical benefits (41), but the effect of LCD on increasing LDL is of concern, albeit balanced by reducing TG level better than LFD. Variations in these effects probably depend on the profile of other nutrients in diets consumed. Most of the reviews concluded that LCD could be used alternatively to LFD for weight loss, but they did not mention any of potential concern of increased LDL-cholesterol in their conclusions, or propose how to avoid this problem, (Table 11). Low CHO dieters may have unlimited intake of fat and protein, including animal-sourced, with long-chain saturated fatty acids which elevate LDL-cholesterol (42). This is in keeping with longer term observational studies reporting detrimental effects of LCDs, increasing risk of CVDs and mortality (43-46).

It is of concern that the present study found that only one of the meta-analysis included reported adverse effects (29). One patient with type 2 diabetes assigned to LCD arm had poor adherence to medication and died in hyperosmolar coma (47). There are many other potential hazards reflected by case reports of LCDs, including Wernicke's encephalopathy (48) and optic neuropathy (49) from thiamine deficiency, acute coronary syndrome (50, 51), keto-acidosis (52) and anxiety disorder (53).

Quality of included meta-analyses and their included RCTs

Strengths of included meta-analyses include the use of PICO to formulate their research questions or objectives of their reviews, using a comprehensive literature search, conduct a

study selection and data extraction in duplicates, and assessing a publication bias. Nonetheless, limitations still exist. Most of them did not report on developing or registering a protocol for their reviews, this could lead to publication bias as they could change data synthesis later to suit their interest (54). Another critical concern is assessing the RoB of included RCTs and impact of the RoB on pooled results as this may limit the validity of their conclusion in both overestimation and underestimation of the true effects (55).

Among meta-analyses that reported the RoB in included RCTs, the quality of included RCTs varied. The primary sources of bias included inadequate reporting of randomisation methods, allocation concealment, lack of blinding outcome assessment and high attrition rate. Although there are two meta-analyses judged as high quality reviews, their pooled results comprised RCTs with mostly high RoB, resulting in limiting the reliability and downgrading the confidence of their results to make a recommendation for guidelines. In addition, interpretation of pooled results should be cautious, as there was publication bias for weight loss and CVD risks across published meta-analyses.

All the meta-analyses included which had funding support declared that the funding body was not involved in any part of the conduct of systematic reviews or meta-analyses. However, our analysis indicates that funding from a commercial company, or potential conflicts of authors, were more evident for those which favoured LCDs rather than LFDs (4 out of 7 meta-analyses), and 75% of these meta-analyses are also of critically low quality, (Table 7). More importantly, a meta-analysis by Naude et al. also found that results from six out of 19 included RCTs were influenced by funders (13). It is always difficult to assess whether funders or conflict of interests of authors influence nutritional study outcomes. A meta-analysis by Chartres et al. demonstrated that outcomes of nutritional studies were more likely to favour industrial sponsors, but that did not reach statistical significance (56).

Impact of published meta-analyses on scientific literature (Scopus and Google Scholar)

Our correlation analysis found that the systematic reviews and meta-analyses with more citations were those published in journals with higher impact factor, but they were papers indicating larger effect size, and worryingly they were papers with lower methodological quality. There is intense scientific debate and media interest in the effects of LCDs, and an apparently greater effect size appears to be overcoming the need for high quality methodology in accepting meta-analyses for publication, and for their subsequent citation as evidence.

Strength and limitation of the present systematic review process

We conducted a review following a written protocol. This systematic review of reviews addresses concordance and discordance in the results of published systematic reviews and meta-analyses. The high quality reviews were highlighted and put together in a single place providing definitive summaries (17). The use of AMSTAR tool provided detailed quality assessment as its items involves the rigorous and transparent steps for conducting a systematic review, and assesses the domains that can produce any biases to the pooled results (21).

Our correlation analyses, examining citations of published systematic reviews has revealed patterns which may be worrying, but we have not attempted to assess the purposes of the documented citations or the interpretations of the results or their influence on practice or policy. The present systematic review of reviews found that only two out of ten meta-analyses are high methodological quality. This highlights the problem that most of systematic reviews could be flawed. Policy decisions should be able to assess the methodological quality before making any recommendations about adopting interventions in clinical practice (16).

We have not attempted any meta-analysis of the published systematic reviews: overlapping of the included RCTs would distort results (18). Our narrative synthesis is a more appropriate way to synthesise results to compare and contrast their methods, quality and conclusions (17). Variables that could influence differences in weight loss between LCD and LFD reported in meta-analyses include the amounts of CHO, duration of intervention, number of subjects and the quality (and possible biases) within the review. However, it is impossible to conduct a multivariable analysis on these predictors because of the small numbers of meta-analyses available.

Implications for practice

The present analysis suggests that LCDs are as effective as LFDs or energy-restricted diets for weight loss in individuals with obesity, but there is some potential risk of unfavourable lipid outcomes with LCDs. The simplicity of LCD makes it easy to follow, but the adherence and attrition rates are similar to more conventional weight loss diets. Although most of the published meta-analyses recommended that LCD could be an alternative approach for weight reduction, we could not make any recommendation for or against the use of LCDs, based on methodological quality, risk of increased LDL-cholesterol and importantly, long-term evidence of clinical outcomes.

Implications for research

It is clear that long term studies with clinical outcomes, not just surrogate markers, are needed. More information about effects of LCD other than metabolic outcomes is also needed especially potential harms such as micronutrient status, bone mineral density and certain type of cancer related to low wholegrain, fibre, or fruits intakes.

This review also highlights potential areas for improving quality of future RCTs by reporting greater details of randomisation process, allocation concealment, blinding outcome assessment and the process to overcome high attrition and low adherence. In addition, conducting a systematic review and meta-analysis of intervention can be improved. We would encourage following guidelines such as the Cochrane Handbook, or Center for Reviews and Dissemination guidance. The RoB assessment and impact of the RoB in pooled results must be reported and discussed, as this is one of most critical components that could impact on the reliability of the results. Including well-conducted RCTs in well-conducted systematic reviews and meta-analyses remains the best approach to define practice and policy.

Conclusion

Published meta-analyses of LCD vs. LFD on weight loss have substantial variation in methods and quality. Reporting of adverse effects is scarce. Most meta-analyses are of rather low methodological quality. Higher quality meta-analyses reported little or no difference in weight loss between the two diets, but publication and citations appear to favour those with apparently large effect-sizes above methodological quality. To aid decision-making, well-conducted systematic reviews of well-conducted RCTs, with reporting of the adverse effects are needed.

Conflict of interest statement

ML has received departmental research support from Novo Nordisk and Diabetes UK, and consultancy fees and support for meeting attendance from Novo-Nordisk, Orexigen, Cambridge Weight Plan, Counterweight Ltd. Other authors have no conflicts of interest to disclose.

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Table Legends:

Table 1. AMSTAR 2 items (21)

Table 2. Characteristics of systematic reviews without meta-analyses

CHO, carbohydrates; RCT, randomised controlled trial.

Table 3. Methods of included systematic reviews without meta-analyses

LCD, low-carbohydrate diet; RCT, randomised controlled trial.

Table 4. Characteristics of included systematic reviews with meta-analyses

BMI, body mass index; CHO, carbohydrates; HP, high protein; LCD, low-carbohydrate diets; VLCKD, very low-carbohydrate ketogenic diets; LFD, low-fat diets; LEARN, Lifestyle, Exercise, Attitudes, Relationships, and Nutrition diets.

Table 5. Methods of included systematic reviews with meta-analyses

WOS, Web of Science; CDSR, Cochrane database for systematic reviews; DARE, Database of Abstracts of Reviews of Effectiveness; RCT, randomised controlled trial; LCD, low-carbohydrate diet; BW, body weight; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; NIH, National Institute of Health; MRC, Medical research council.

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Pharma Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Ono Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd.

Table 6. Quality assessment and overall rating judgement of published systematic reviews with meta-analyses

MA, meta-analysis

Table 7. Weight loss outcome (kilograms)

LCD, low-carbohydrate diet; LFD, low-fat diet; CHO, carbohydrates; E, energy; F, fat; P, protein; VLCKD, very low-carbohydrate ketogenic diet; T2DM, type 2 diabetes mellitus.

[a] Weight loss are shown in mean difference between LCDs and LFD/energy-restricted diets with 95% confidence interval in parenthesis. Values represent mean weight change in LCD minus mean weight change in LFD; negative values indicate subjects following LCD lost more weight than those who followed LFD.

[b] Results from network meta-analysis, heterogeneity was calculated from direct comparison of 4 trials comparing LCD vs. LFD at 12 months, I2=85.5%.

Table 8. AMSTAR quality, number of studies, number of subjects and effect size

[a] excludes one study of network meta-analysis due to indirect comparison of interventions

[b] for meta-analysis with multiple time-points (e.g. 6 and 12 months) or population (e.g. with and without diabetes), the mean difference from highest number of included RCTs was presented and used for correlation coefficient analysis.

[c] values represent mean weight loss in LCD minus mean weight loss in LFD; negative values indicate subjects following LCD lost weight greater than those who followed LFD.

[d] Spearman's rank correlation coefficient analysis

[e] Pearson's correlation coefficient analysis

Table 9. AMSTAR quality, effect size and citation counts

[a] for meta-analysis with multiple time-points (e.g. 6 and 12 months) or population (e.g. with and without diabetes), the mean difference from highest number of included RCTs was presented and used for correlation coefficient analysis.

[b] values represent mean weight loss in LCD minus mean weight loss in LFD; negative values indicate subjects following LCD lost more weight than those who followed LFD.

Table 10. Correlation coefficient between 3-year citation counts and quality, mean difference in weight loss, and impact factor.

Table 11. Conclusions from systematic reviews with meta-analyses of LCD vs. LFD/energy-restricted diets

LCD, low-carbohydrate diet; LFD, low-fat diet; CVD, cardiovascular disease; VLCKD, very low-carbohydrate ketogenic diet; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ASCVD, atherosclerotic cardiovascular disease.

Figure legend:

Figure 1. Flow diagram of study selection process

WoS, Web of Sciences; CDSR, Cochrane database for systematic reviews

Table 1. AMSTAR 2 items (21)

Critical domains
• *Item 4. Did the review authors use a comprehensive literature search strategy?* • *Item 9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?* • *Item 11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?* • *Item 12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?* • *Item 13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?* • *Item 14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?* • *Item 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*
Non-critical domains
• *Item 1. Did the research questions and inclusion criteria for the review include the components of PICO?* • *Item 2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?* • *Item 3. Did the review authors explain their selection of the study designs for inclusion in the review?* • *Item 5. Did the review authors perform study selection in duplicate?* • *Item 6. Did the review authors perform data extraction in duplicate?* • *Item 7. Did the review authors provide a list of excluded studies and justify the exclusions?* • *Item 8. Did the review authors describe the included studies in adequate detail?* • *Item 10. Did the review authors report on the sources of funding for the studies included in the review?* • *Item 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?*

Table 2. Characteristics of systematic reviews without meta-analyses

Authors	Population/ Condition	Pre-specified low-carbohydrate diets	Pre-specified control diets (low-fat or energy restricted diets)	Duration of intervention
Castaneda-Gonzalez 2011 (22)	Adults with Type 2 diabetes	Maximum intake of 130 g of CHO per day	No, defined as RCTs' authors definition	at least 12 weeks or 4 months
Dutton 2014 (23)	Adults with overweight/obesity as defined by trials authors	No, defined as RCTs' authors definition	No, defined as RCTs' authors definition	at least 2 months

CHO, carbohydrates; RCT, randomised controlled trial.

Table 3. Methods of included systematic reviews without meta-analyses

Authors	Databases	Search time frame	Included studies	No. of subjects	Risk of Bias Assessment	Publication bias	Funding source	Authors' declaration
Castaneda-Gonzalez 2011 (22)	PubMed, Cochrane and EBCOhost	1 Jan 2000 to 1 Jan 2010	8	664	Assessed randomization process, and intention to treat as part of quality assessment.	N/A	Did not report	Did not report
Dutton 2014 (23)	PubMed	Jan 2003 to April 2014	10 RCTs of LCD intervention	N/A	Did not perform/report	N/A	Did not report	No conflict of interest

LCD, low-carbohydrate diet; RCT, randomised controlled trial.

Table 4. Characteristics of included systematic reviews with meta-analyses.

Authors	Population/ Condition	Pre-specified low-carbohydrate diets	Pre-specified control diets (low-fat or energy restricted diets)	Duration of intervention
Nordmann 2006 (10)	BMI ≥ 25 kg/m^2	Maximum intake of 60 g of CHO per day without energy intake restriction	Maximum of 30% of the daily energy intake from fat with energy intake restriction	at least 6 months
Hession 2009 (27)	Mean or median BMI of 28 kg/m^2	• HP 'ketogenic' diet, CHO content was less than 40 g/day, irrespective of energy content. • LCDs, CHO 60 g/day.	LFD (30% or less daily energy from dietary fat) – 600 kcal deficit diet.	at least 6 months
Hu 2012 (28)	Adults with overweight/obesity as defined by trials authors	≤45% of energy from CHO	≤30% of energy from fat	at least 6 months
Bueno 2013 (25)	Mean BMI > 27.5 kg/m^2	VLCKD (i.e. a diet with no more than 50 g CHO/day or 10% of daily energy from CHO)	Restricted-energy diet with less than 30 % of energy from fat	> 12 months
Johnston 2014 (29)	BMI ≥ 25 kg/m^2	Atkins, South Beach, Zone; ≤40%CHO, approximately 30%Protein, 30-55%Fat	Ornish, Rosemary Conley; 60%CHO, 10-15%Protein, ≤20%Fat	3 months or Longer
Naude 2014 (13)	Adults with overweight/obesity have diabetes, glucose intolerance or insulin resistance, cardiovascular conditions or risk factors such as hypertension and dyslipidaemia, as defined by trial authors	<45%CHO: a) low CHO, high fat, high protein diet (high fat variant) or b) low CHO, recommended fat, high protein diet (high protein variant)	Control diets were balanced weight loss diet plans - energy restriction, Fat 25-35%, CHO 45-65%, Protein 10-20%	12 weeks up 1) 3-6 months 2) 1-2 years
Alexandraki 2015 (24)	BMI ≥ 25 kg/m^2	<45% of energy from CHO; Atkins, Zone diets. Some studies had 2 interventions to compare e.g. Atkins vs. Ornish, Atkins vs. LEARN diets	<30% of energy from fat was classified as an LFD. Weight Watcher, Slim Fast, Rosemary Conley, Ornish, LEARN diets	at least 6 months
Sackner-Bernstein 2015 (14)	Adults with overweight/obesity as defined by trials' authors. Excluded RCTs with subjects had co-morbidity other than dyslipidemia	Total CHO intake ≤120 g/day.	Institute of Medicine's report in 2002 (≤30% of energy from fat/day)	not specific
Hashimoto 2016 (26)	Adults with overweight/obesity as defined by trials' authors.	No, defined as RCTs' authors definition	No, use statement 'control group'	not specific
Mansoor 2016 (12)	Reported healthy adults with overweight/obesity. Excluded RCTs conducted solely on subjects with BMI ≥ 35 kg/m^2	Reference to the Atkins diet, only 20–40 g/d of CHO in the first phase or CHO intake of <20% of total energy intake.	Conventional LFD. - not define by % or grams of fat content	at least 6 months

BMI, body mass index; CHO, carbohydrates; HP, high protein; LCD, low-carbohydrate diets; VLCKD, very low-carbohydrate ketogenic diets; LFD, low-fat diets; LEARN, Lifestyle, Exercise, Attitudes, Relationships, and Nutrition diets.

Table 5. Methods of included systematic reviews with meta-analyses

Authors	Databases	Search time frame	Included studies	No. of subjects	Risk of Bias Assessment	Publication bias	Funding source	Authors' declaration
Nordmann 2006 (10)	MEDLINE, EMBASE, PASCAL, GLOBAL HEALTH, HEALTH, WOS, and the Cochrane Library	1 January 1980 to 28 February 2005	5	447	Allocation concealment, blinded outcome assessment, loss to follow-up, and full descriptions of losses to follow-up and withdrawals were assessed. None of the trials used blinded outcome assessment for weight loss.	Small number of trials precluded a sensitive evaluation of publication bias, although no detection of this bias by funnel plot.	Swissmilk, Berne, Switzerland	WS Yanci Jr's salary is funded in part by the Robert C Atkins Foundation
Hession 2009 (27)	MEDLINE, EMBASE, BIOSIS, Commonwealth Agricultural Bureau Nutrition, Abstracts and Reviews, CENTRAL, DARE, CRD database of systematic reviews, PsycINFO, WOS, UK National Research Register, CINAHL, HealthSTAR, AMED, SPORTDiscus, British Library Inside	January 2000 to March 2007	13	1222	Methodological quality was assessed using a standard form and including intention to treat basis. Authors did not state the use of Cochrane risk of bias tool. In result section, they also did not report quality assessment of the included trials.	Did not report on publication bias assessment.	Hession M was supported by a commercial grant by LighterLife	No conflict of interest was declared
Hu 2012 (28)	MEDLINE, EMBASE, WOS, CDSR	1966 - 2011	23	2788	Blinding, loss to follow-up and intention to treat were assessed. Did not assess method of randomization and allocation concealment. Authors did not state the use of Cochrane risk of bias tool. In result section, they also did not report quality assessment of the included trials.	Possible for BW, TG, TC, LDL, HDL, insulin	Dr. Bazzano was supported by grant K08 HL091108 from the NIH/ National Heart, Lung, and Blood Institute, USA	No conflict of interest was declared
Bueno 2013 (25)	MEDLINE, CENTRAL, ScienceDirect, Scopus, LILACS, SciELOand ClinicalTrials.gov. In addition, the following grey literature databases were searched: OpenGrey.eu, DissOnline.de, NYAM.org and ClinicalEvidence.com	up to August 2012	13	1577	Cochrane Collaboration Risk of Bias Tool. 9 of 13 RCTs were of low risk of bias. Allocation concealment and blinding outcome assessment were of unclear to high risk of bias.	Possible for TG level. No publication bias for BW, LDL, HDL, and blood pressure.	A studentship to the first author by Conselho Nacional de Pesquisa e Desenvolvimento Cientı´fico e Tecnolo´gico (CNPq) grant 130639/2011-7	No conflict of interest was declared
Johnston 2014 (29)	AMED, CDSR, CENTRAL, CINAHL, EMBASE, and MEDLINE from inception of each database to April 2014	up to April 2014	48	7286	Allocation concealment, sequence generation, blinding to patient and assessor, missing participant outcome data. 13 of 33 RCTs of LCD were high risk of bias.	Funnel plot found asymmetry of weight loss outcome by Atkins diet vs. moderate macronutrient diets.	Canadian Institute of Health Research.	No conflict of interest was declared
Naude 2014 (13)	MEDLINE (PubMed), EMBASE, CENTRAL	last search on 19 March 2014	19	3209	Cochrane Collaboration Risk of Bias Tool. 50% of trials were unclear or high risk of bias on selection bias, detection bias and attrition bias. Six trials found to be influenced by funder	Possible for BW, LDL, HDL, TG, TC	Effective Health Care Research Consortium and the South African MRC	No conflict of interest was declared

Alexandraki 2015 (24)	MEDLINE (PubMed)	1 January 2001 to October 2014	17	1958	Cochrane Collaboration Risk of Bias Tool. (16 were high risk of bias, 1 was at unclear risk of bias). Lack of allocation concealment and incomplete outcome data due to high attrition.	Did not report on publication bias assessment.	No financial relationships to disclose	No conflict of interest was declared
Sackner-Bernstein 2015 (14)	MEDLINE (PubMed)	1966 - 2014	17	1797	No explicit risk of bias assessment was reported.	Possible for BW	Atkins Nutritionals under contract to ExVivos, LLC (ExVivos, LLC is owned by the first author).	See 1
Hashimoto 2016 (26)	MEDLINE, EMBASE and CDSR.	up to December 2014	14	1805 (1416 after exclude dropout)	GRADE, AMSTAR. No use of Cochrane Collaboration Risk of Bias Tool.	Possible for BW	No funding for this study	See 2
Mansoor 2016 (12)	MEDLINE via Ovid, EMBASE and CENTRAL	up to 28 May 2015	11	1369	Cochrane Collaboration Risk of Bias Tool. One trial was high risk of bias. Most of trials did not report on allocation concealment.	Possible for BW, TC, LDL, SBP, DBP and glucose.	The Throne Holst Foundation for Nutrition Research and University of Oslo.	No conflict of interest was declared

WOS, Web of Science; CDSR, Cochrane database for systematic review; DARE, Database of Abstracts of Reviews of Effectiveness; RCT, randomised controlled trial; LCD, low-carbohydrate diet; BW, body weight; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; NIH, National Institute of Health; MRC, Medical research council.
1. Jonathan Sackner-Bernstein owns and may receive compensation from ExVivos, LLC. ExVivos, LLC provided payment to authors (DK and SK) for their role as contractors to ExVivos, LLC.
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Table 6. Quality assessment and overall rating judgement of published systematic reviews with meta-analyses

	1. Did the research questions and inclusion criteria for the review include the components of PICO?	2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	3. Did the review authors explain their selection of the study designs for inclusion in the review?	4. Did the review authors use a comprehensive literature search strategy?	5. Did the review authors perform study selection in duplicate?	6. Did the review authors perform data extraction in duplicate?	7. Did the review authors provide a list of excluded studies and justify the exclusions?	8. Did the review authors describe the included studies in adequate detail?	9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	10. Did the review authors report on the sources of funding for the studies included in the review?	11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	**Overall rating judgement**
Castaneda-Gonzalez 2011 (22)	Yes	No	Yes	Partial yes	No	No	No	Partial yes	No	No	No MA	No MA	No	Yes	No MA	No	***Critically low***
Dutton 2014 (23)	Yes	No	No	No	No	No	No	Partial yes	No	No	No MA	No MA	No	No	No MA	Yes	***Critically low***
Nordmann 2006 (10)	Yes	No	No	Partial yes	Yes	Yes	No	No	Partial yes	No	Yes	No	Yes	Yes	Yes	Yes	***Moderate***
Hession 2009 (27)	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	Yes	***Critically low***
Hu T 2012 (28)	Yes	No	yes	Partial yes	Yes	Yes	No	yes	No	No	Yes	No	No	Yes	Yes	Yes	***Critically low***
Bueno NB 2013 (25)	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	***High***
Johnston 2014 (29)	Yes	No	No	Yes	Yes	Yes	No	Yes	Partial yes	No	Yes	Yes	Yes	Yes	Yes	Yes	***Moderate***
Naude 2014 (13)	Yes	yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	***High***
Alexandraki 2015 (24)	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	***Critically low***
Sackner-Bernstein 2015 (14)	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Yes	***Critically low***
Hashimoto 2016 (26)	Yes	No	No	Partial yes	Yes	Yes	No	Yes	No	No	No	No	Yes	No	Yes	Yes	***Critically low***
Mansoor 2016 (12)	Yes	Yes	No	Partial yes	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	***Moderate***

MA, meta-analysis

Table 7. Weight loss outcome (kilograms)

Authors	Pre-specified LCD	Pre-specified LFD / energy-restricted diet	Commercial support	AMSTAR 2 Quality	6 months [a]	12 months [a]	No specific time point [a]
Nordmann 2006 (10)	60 g CHO/day	30%E fat	Yes	Moderate	-3.3 (-5.3 to -1.4) I^2=65%, p=0.02	-1.0 (-3.5 to 1.5) I^2=48%, p=0.15	-
Hession 2009 (27)	HP ketogenic 40 g CHO LCD 60 g CHO	30%E fat	Yes	Critically low	-4.02 (-4.54 to -3.49) I^2=77.3%, p<0.0001	-1.05 (-2.09 to -0.01) I^2=10.5%, p=0.35	-
Hu 2012 (28)	45%E CHO	30%E fat	No	Critically low	-	-	-1.0 (-2.2 to 0.2) I^2=85.7, p<0.001
Bueno 2013 (25)	VLCKD 50 g or 10%E CHO	30%E fat	No	High	-	-0.91 (-1.65 to -0.17) I^2=0%, p=0.47	-
Johnston 2014 (29)	40%E CHO	20%E fat	No	Moderate	-0.74 (-2.31 to 0.78)[b]	0.02 (-1.78 to 1.79)[b]	-
Naude 2014 (13)	45%E CHO	Balanced weight loss diet (45-65%CHO, 25-35%F, 10-20%P)	No	High	without T2DM: -0.74 (-1.49 to 0.01) I^2=53%, p=0.009 with T2DM: 0.82 (-1.25 to 2.90) I^2=0%, p=0.93	without T2DM: -0.48 (-1.44 to 0.49) I^2=12%, p=0.34 with T2DM: 0.91 (-2.08 to 3.89) I^2=33%, p=0.21	-
Alexandraki 2015 (24)	45%E CHO	30%E fat	No	Critically low	-1.44 (-2.32 to -0.56) I^2=91%, p<0.001	-0.77 (-1.36 to -0.18) I^2=48%, p=0.01	-
Sackner-Bernstein 2015 (14)	120 g CHO	30%E fat	Yes	Critically low	-	-	-2.04 (-3.15 to -0.93) no I^2 calculated
Hashimoto 2016 (26)	No; based on RCTs' authors defined.	No	Yes	Critically low	-	-	-0.7 (-1.07 to -0.33) I^2=90.3%, p<0.0001
Mansoor 2016 (12)	Atkins type, 20-40 g CHO in first phase, or 20%E CHO	Conventional LFD; did not define % fat	No	Moderate	-	-	-2.17 (-3.36 to -0.99) I^2=82.2%, p<0.0001

LCD, low-carbohydrate diet; LFD, low-fat diet; CHO, carbohydrates; E, energy; F, fat; P, protein; VLCKD, very low-carbohydrate ketogenic diet; T2DM, type 2 diabetes mellitus.
[a] Weight loss are shown in mean difference between LCDs and LFD/energy-restricted diets with 95% confidence interval in parenthesis. Values represent mean weight change in LCD minus mean weight change in LFD; negative values indicate subjects following LCD lost more weight than those who followed LFD.
[b] Results from network meta-analysis, heterogeneity was calculated from direct comparison of 4 trials comparing LCD vs. LFD at 12 months, I^2=85.5%.

Table 8. AMSTAR quality, number of studies, number of subjects and effect size

Published meta-analyses [a]	AMSTAR quality score	No. of primary studies	No. of subjects	Mean difference in weight loss (kg) [b, c]
Naude 2014 (13)	14	14	1745	-0.74
Bueno 2013 (25)	13	13	1577	-0.91
Hu 2012 (28)	9.5	23	2788	-1.00
Mansoor 2016 (12)	9.5	11	1369	-2.17
Nordmann 2006 (10)	9	5	447	-3.30
Alexandraki 2015 (24)	8	24	1958	-1.44
Hashimoto 2016 (26)	7	14	1416	-0.70
Hession 2009 (27)	5	9	690	-4.02
Sackner-Bernstein 2015 (14)	4	17	1797	-2.04

Items		Correlation coefficient
Mean difference in weight loss between LCD & LFD	Quality score [d]	rho = 0.41, p=0.27
	No. of primary studies [e]	r = 0.60, p=0.09
	No. of subjects [e]	*r = 0.73, p=0.03*

[a] excludes one study of network meta-analysis due to indirect comparison of interventions
[b] for meta-analysis with multiple time-points (e.g. 6 and 12 months) or population (e.g. with and without diabetes), the mean difference from highest number of included RCTs was presented and used for correlation coefficient analysis.
[c] values represent mean weight loss in LCD minus mean weight loss in LFD; negative values indicate subjects following LCD lost weight greater than those who followed LFD.
[d] Spearman's rank correlation coefficient analysis
[e] Pearson's correlation coefficient analysis

Table 9. AMSTAR quality, effect size and citation counts

Published meta-analysis	AMSTAR quality score	Mean difference in weight loss (kg) [a, b]	3-year citation counts after publication		Impact factor (at year 3 of publication)
			Scopus	Google Scholar	
Naude 2014 (13)	14	-0.74	43.90	64.10	2.806
Bueno 2013 (25)	13	-0.91	63.47	102.32	3.311
Hu 2012 (28)	9.5	-1.00	67.26	104.21	5.23
Nordmann 2006 (10)	9	-3.30	133.04	188.61	9.11
Hession 2009 (27)	5	-4.02	73.53	119.49	7.038

[a] for meta-analysis with multiple time-points (e.g. 6 and 12 months) or population (e.g. with and without diabetes), the mean difference from highest number of included RCTs was presented and used for correlation coefficient analysis.
[b] values represent mean weight loss in LCD minus mean weight loss in LFD; negative values indicate subjects following LCD lost more weight than those who followed LFD.

Table 10. Correlation coefficient between 3-year citation counts and quality, mean difference in weight loss, and impact factor.

Items	Spearman's rank correlation coefficient	
	Scopus	Google Scholar
Citation counts & Quality score	*-0.90, p=0.037*	*- 0.90, p=0.037*
Citation counts & Mean difference in weight loss	*-0.90, p=0.037*	*-0.90, p=0.037*
Citation counts & Impact factor	*1.00, p=0.01*	*1.00, p=0.01*

Table 11. Conclusions from systematic reviews with meta-analyses of LCD vs. LFD/energy-restricted diets

Authors	Finding/Conclusion	AMSTAR 2 Quality
Naude 2014 (13)	Short-term weight loss was demonstrated in both LCDs and balanced diets. For Up to 2 years, weight loss and CVD risk factors were little or no difference in adults with overweight or obesity, with or without type 2 diabetes, who were randomised to LCDs or isoenergetic balanced weight loss diets.	High
Bueno 2013 (25)	The VLCKD achieved greater reductions in body weight, diastolic blood pressure, and TG, but more rises in LDL and HDL when compared to LFD. Therefore, VLCKD may be another option for weight management. Further studies are needed to examine the effects beyond blood parameters.	High
Johnston 2014 (29)	LCD and LFD programmes achieved weight loss greater than no dietary intervention through the influences of behavioural support and exercise. Weight loss differences among named diets were also small and of little importance. This supports recommendation of any diets that patients could adhere to lose weight.	Moderate
Mansoor 2016 (12)	LCDs showed inconsistent changes in two CVD risk factors – leading to more weight loss yet increased LDL. Weight loss following LCDs needs to be weighed against unfavourable change of increased LDL.	Moderate
Nordmann 2006 (10)	LCD was as effective as LFD for weight loss for up to 1 year. However, favourable changes in TG and HDL should be weighed against increased LDL.	Moderate
Hu 2012 (28)	LCD was as effective as LFD for weight loss and metabolic risk factors, and could be recommended for weight reduction. Longer-term studies on clinical CVD events are needed.	Critically low
Alexandraki 2015 (24)	Weight loss could be achieved by carbohydrate restriction. However, weight loss differences between LCDs and LFDs were very small and of little importance. Further studies are needed.	Critically low
Hashimoto 2016 (26)	Greater weight and body fat mass loss were achieved in LCDs than control diets. Further studies are needed due to an insufficient number of participants and duration of study follow up period, as well as possible publication bias.	Critically low
Hession 2009 (27)	LCDs achieved greater weight loss and CVD risk reduction at 6 months, and were as effective as LFDs for up to 1 year. More long-term studies are needed on CVD benefits.	Critically low
Sackner-Bernstein 2015 (14)	Although both LCDs and LFDs achieved significant weight loss and reduction of predicted ASCVD risk, LCDs were more effective for up to 2 years. This support dietary guideline should re-consider LCD as effective and safe dietary intervention, although longer-term studies are needed.	Critically low

LCD, low-carbohydrate diet; LFD, low-fat diet; CVD, cardiovascular disease; VLCKD, very low-carbohydrate ketogenic diet; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ASCVD, atherosclerotic cardiovascular disease.

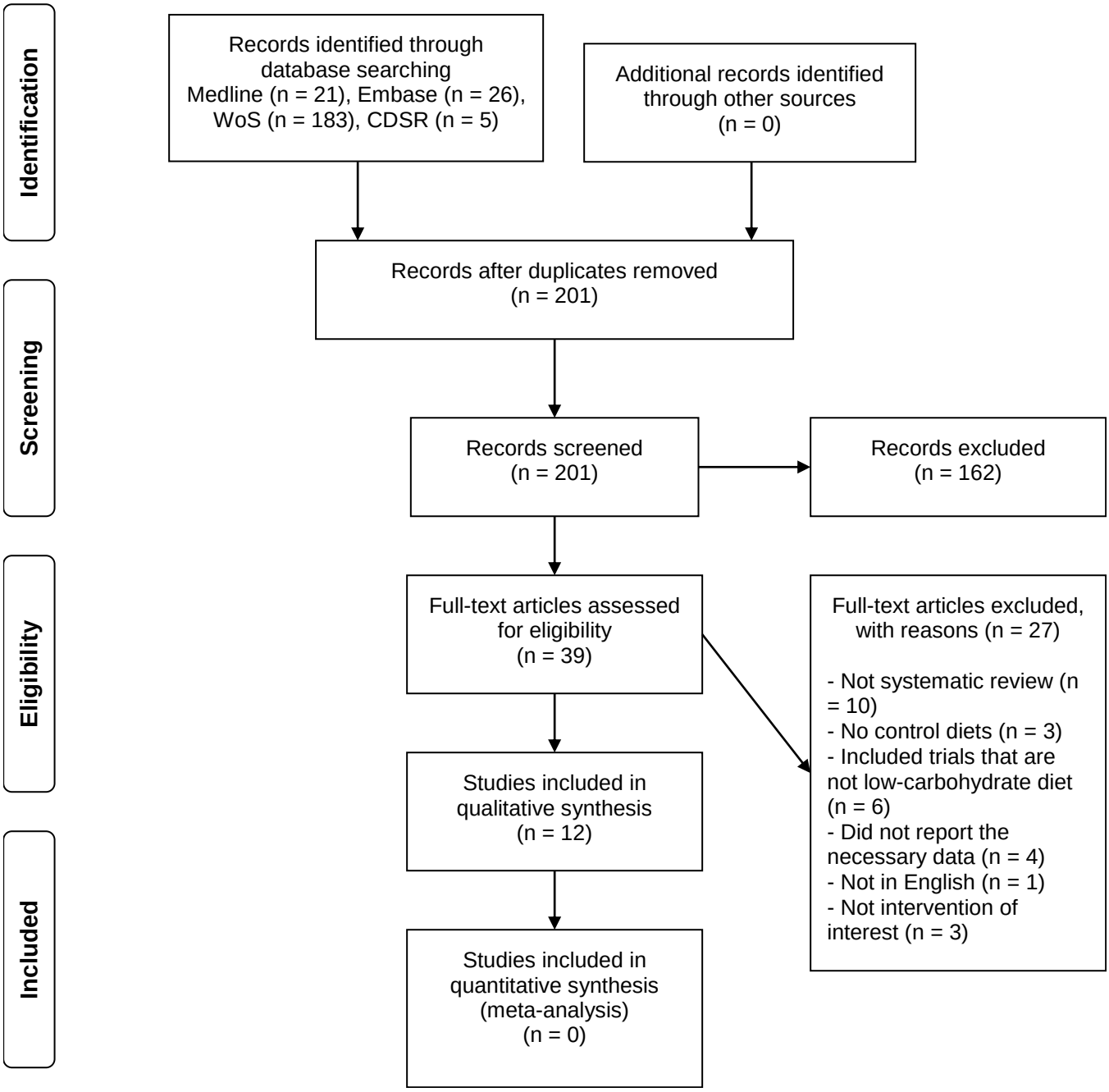

Figure 1 Flow diagram of study selection process

WoS, Web of Sciences; CDSR, Cochrane database for systematic review

Table S1. Search strategy for MEDLINE (Ovid)

Search terms	Date searched
1. diet, carbohydrate-restricted/ or diet, paleolithic/ or ketogenic diet 2. Weight Loss/ 3. "review"/ 4. meta-analysis/ 5. low carbohydrate diet.mp. 6. very low carbohydrate diet.mp. 7. zone diet.mp. 8. sugar busters diet.mp. 9. harcombe diet.mp. 10. weight reduction.mp. 11. systematic review.mp. 12. meta analysis.mp. 13. 1 or 5 or 6 or 7 or 8 or 9 14. 2 or 10 15. 3 or 4 or 11 or 12 16. 13 and 14 and 15 17. limit 16 to (english language and yr="2000 -Current")	27th September 2017

Table S2. Full-texts excluded from analysis and reasons for exclusion

Source	Reason for exclusion
Anton *et al.* (1)	No control diets
Atallah *et al.* (2)	Did not report necessary data, reported change from baseline
Avenell *et al.* (3)	Mostly low-fat diets
Bravata *et al.* (4)	Did not report necessary data, reported pooled results of mixed study designs.
Bray *et al.* (5)	Not systematic review
Brehm *et al.* (6)	Not systematic review
Chaudhry *et al.* (7)	No control diets, counselling is a control group
Clifton *et al.* (8)	Included trials that are not low-carbohydrate diets.
Dong *et al.* (9)	Included trials that are not low-carbohydrate diets.
Dyson (10)	Not systematic review, invited review
Dyson (11)	Not systematic review, included single arm trial
Esposito *et al.* (12)	Included trials that are not low-carbohydrate diets
Franz *et al.* (13)	Mixed intervention, not clear; low-carbohydrate diets are not the primary focus.
Hall *et al.* (14)	Not systematic review
Hu *et al.* (15)	Not systematic review, invited review
Kirk *et al.* (16)	No control diets
Kosinski *et al.* (17)	Not systematic review
Lepe *et al.* (18)	Included trials that are not low-carbohydrate diets. Focused on hi-protein diets
Mancini *et al.* (19)	Included trials that are not low-carbohydrate diets.
Martinez *et al.* (20)	Not systematic review
Mencia *et al.*(21)	Not English language
Santos *et al.* (22)	Did not report necessary data, reported change from baseline
Schwingshackl *et al.* (23)	Low-carbohydrate diet is not a primary intervention of interest of the review, weight loss is not a primary outcome.
Schwingshackl *et al.* (24)	Included trials that are not low-carbohydrate diets.
Soeliman *et al.* (25)	Did not report necessary data, no weight loss outcome
Wood (26)	Not systematic review
Wood *et al.* (27)	Not systematic review

Table S3. Triglyceride (mmol/L)

Author Year		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Nordmann 2006 [28]		4	-0.25	-0.43 to -0.06	48%	0.13	3	-0.35	-0.67 to -0.03	59%	0.09
Hession 2009 [29]		9	-0.16	-0.24 to -0.08	96.4%	<0.00001	5	-0.19	-0.36 to -0.01	68.2%	0.01
Naude 2014 [30]											
No DM	*HF*	8	-0.03	-0.13 to 0.07	79%	<0.0001	4	-0.06	-0.15 to 0.03	0%	0.9
	HP	4	-0.15	-0.37 to 0.08	27%	0.25	2	-0.02	-0.34 to 0.31	18%	0.27
	Total	12	-0.05	-0.14 to 0.04	72%	<0.0001	6	-0.06	-0.14 to 0.03	0%	0.86
with DM	*HF*	1	-0.3	-0.93 to 0.33	-[1]	-[1]	1	-0.2	-0.63 to 0.23	-[1]	-[1]
	HP	3	-0.18	-0.45 to 0.09	0%	0.87	2	0.13	-0.45 to 0.70	0%	0.44
	Total	4	-0.20	-0.45 to 0.05	0%	0.94	3	-0.08	-0.43 to 0.26	0%	0.50
Bueno 2013 [31]		-	-	-	-	-	12	-0.18	-0.27 to -0.08	12%	0.33

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu 2012 [32]	20	-0.16	-0.22 to -0.10	55.6%	0.07
Sackner-Bernstein 2015 [33]	NR	-0.33	-0.44 to -0.21	NR	NR
Mansoor 2015 [34]	11	-0.26	-0.37 to -0.15	63.8%	0.002

NR, not reported; DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate

[1] no heterogeneity calculated, only one study.

Table S4. LDL-cholesterol (mmol/L)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Nordmann 2006 [28]		4	0.14	0.03 to 0.26	0%	0.66	3	0.20	0.05 to 0.36	0%	0.8
Hession 2009 [29]		8	0.14	0.08 to 0.2	0%	0.61	4	0.37	0.28 to 0.46	92.8%	<0.00001
Naude 2014 [30]											
No DM	*HF*	8	0.09	-0.02 to 0.20	52%	0.04	4	0.07	-0.05 to 0.18	18%	0.3
	HP	4	0.12	-0.11 to 0.34	0%	0.67	2	0.01	-0.26 to 0.29	0%	0.5
	total	12	0.09	0.00 to 0.18	32%	0.14	6	0.07	-0.01 to 0.16	0%	0.5
with DM	*HF*	1	0.20	-0.18 to 0.58	- [1]	- [1]	1	0.30	-0.05 to 0.65	- [1]	- [1]
	HP	4	0.02	-0.20 to 0.23	39%	0.18	3	0.05	-0.14 to 0.23	0%	0.50
	total	5	0.06	-0.11 to 0.23	25%	0.26	4	0.10	-0.06 to 0.27	0%	0.40
Bueno 2013 [31]		-	-	-	-	-	12	0.12	0.04 to 0.20	0%	0.70

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu 2012 [32]	19	0.10	0.03 to 0.17	50%	0.01
Sackner-Bernstein 2015 [33]	NR	0.22	0.09 to 0.35	NR	NR
Mansoor 2015 [34]	11	0.16	0.003 to 0.33	84%	0.000

NR, not reported; DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate

[1] no heterogeneity calculated, only one study.

Table S5. HDL-cholesterol (mmol/L)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Nordmann 2006 [28]		4	0.12	0.04 to 0.21	75%	0.01	3	0.08	-0.02 to 0.18	79%	0.01
Hession 2009 [29]		9	0.04	0.00 to 0.07	0%	0.62	5	0.06	0.02 to 0.11	0%	0.49
Naude 2014 [30]											
No DM	*HF*	8	0.03	-0.03 to 0.08	76%	0.0001	4	0.02	-0.01 to 0.06	29%	0.24
	HP	4	0.07	-0.02 to 0.16	0%	0.95	3	0.09	0.03 to 0.15	0%	0.82
	total	12	0.03	-0.01 to 0.08	63%	0.002	7	0.04	0.01 to 0.08	35%	0.16
with DM	*HF*	1	0.11	-0.13 to 0.35	- [1]	- [1]	1	0.16	-0.03 to 0.35	- [1]	- [1]
	HP	4	-0.01	-0.06 to 0.03	0%	0.65	3	-0.04	-0.1 to 0.02	0%	0.84
	total	5	-0.01	-0.05 to 0.04	0%	0.62	4	-0.00	-0.09 to 0.08	26%	0.25
Bueno 2013 [31]		-	-	-	-	-	12	0.09	0.06 to 0.12	9%	0.36

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu Tien 2012 [32]	19	0.09	0.05 to 0.12	78.6%	<0.001
Sackner-Bernstein 2015 [33]	NR	0.13	0.09 to 0.17	NR	NR
Mansoor 2015 [34]	11	0.14	0.09 to 0.19	76.3%	0.000

NR, not reported; DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate

[1] no heterogeneity calculated, only one study.

Table S6. Total cholesterol (mmol/L)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Nordmann 2006 [28]		4	0.23	0.08 to 0.37	0%	0.48	3	0.26	0.09 to 0.42	0%	0.63
Hession 2009 [29]		9	0.19	0.1 to 0.28	0%	0.84	4	0.2	-0.1 to 0.3	46%	0.14
Naude 2014 [30]											
No DM	*HF*	8	0.06	-0.04 to 0.16	30%	0.19	4	0.04	-0.11 to 0.19	30%	0.23
	HP	4	0.15	-0.10 to 0.40	29%	0.24	2	0.1	-0.17 to 0.38	0%	0.44
	total	12	0.08	-0.02 to 0.17	26%	0.19	6	0.06	-0.03 to 0.16	0%	0.42
with DM	*HF*	1	0.2	-0.35 to 0.75	- [1]	- [1]	1	0.40	-0.05 to 0.85	- [1]	- [1]
	HP	4	-0.00	-0.32 to 0.31	56%	0.08	3	0.03	-0.18 to 0.25	0%	0.54
	total	5	0.04	-0.21 to 0.30	43%	0.14	4	0.10	-0.12 to 0.31	9%	0.35

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu Tien 2012 [32]	15	0.07	0.02 to 0.12	20%	0.45
Sackner-Bernstein 2015 [33]	NR	0.24	0.07 to 0.41	NR	NR
Mansoor 2015 [34]	4	0.26	-0.09 to 0.62	82%	0.001

NR, not reported; DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate

[1] no heterogeneity calculated, only one study.

Table S7. Blood glucose (mmol/L)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hession 2009 [29]		6	-0.01 no unit	-0.15 to 0.13	47.5%	0.09	4	-0.05	-0.2 to 0.11	0%	0.56
Naude 2014 [30]											
No DM	*HF*	6	0	-0.12 to 0.13	66%	0.01	4	0.07	-0.1 to 0.23	60%	0.06
	HP	4	0.18	0.02 to 0.35	0%	0.74	2	-0.21	-0.44 to 0,02	0%	0.33
	total	10	0.05	-0.05 to 0.15	54%	0.02	6	-0.00	-0.16 to 0.16	64%	0.02
with DM	*total*	2	0.69	-0.02 to 1.40	18%	0.27	1	0.00	-1.94 to 1.94	- [1]	- [1]
Bueno 2013 [31]		-	-	-	-	-	8	-0.08	-0.18 to 0.02	0%	0.88

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu 2012 [32]	14	-0.02	-0.11 to 0.07	41.2%	0.06
Mansoor 2015 [34]	7	-0.23	-0.55 to 0.08	91.5%	0.000

DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate
[1] no heterogeneity calculated, only one study.

Table S8. Insulin

Authors	time point	number of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu 2012 [32]	6-24 months	12	-0.1 IU/mL	-0.8 to 0.6	7.8%	0.29
Bueno 2013 [31]	>/= 12 months	6	-5.52 pmol/l	-13.62 to 2.57	26%	0.24
Mansoor 2015 [34]	6-24 months	7	-0.11 mU/l	-1.49 to 1.26	87.5%	<0.001

Table S9. HbA1c (%)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Naude 2014 [30]											
with DM	*HF*	1	0.4	-0.50 to 1.30	- [1]	- [1]	1	0.10	-1.46 to 1.66	- [1]	- [1]
	HP	4	0.18	-0.02 to 0.39	0%	0.81	3	0.01	-0.29 to 0.30	0%	0.99
	total	5	0.19	-0.00 to 0.39	0%	0.88	4	0.01	-0.28 to 0.30	0%	1.00
Bueno 2013 [31]		-	-	-	-	-	4	-0.24	-0.55 to 0.06	0%	0.59

DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate
[1] no heterogeneity calculated, only one study.

Table S10. Systolic blood pressure (mmHg)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I^2	p-value for I^2	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Nordmann 2006 [28]		5	-2.4	-4.9 to 0.1	0%	0.76	3	-1.3	-4.5 to 2	0%	0.57
Hession 2009 [29]		6	-1.35	-3.25 to 0.56	19.9%	0.28	5	-2.19	-4.35 to -0.03	28.2%	0.23
Naude 2014 [30]											
No DM	*HF*	5	-1.41	-2.9 to 0.08	0%	0.64	4	-1.38	-4.07 to 1.32	35%	0.2
	HP	2	-0.79	-7.32 to 5.74	27%	0.24	2	-6.45	-21.01 to 8.10	77%	0.04
	total	7	-1.26	-2.67 to 0.15	0%	0.64	6	-2.00	-5.00 to 1.00	48%	0.09
with DM	*HF*	1	-2.00	-9.41 to 5.41	- [1]	- [1]	1	1.00	-5.79 to 7.79	- [1]	- [1]
	HP	3	1.30	-3.46 to 6.06	55%	0.11	3	0.07	-3.87 to 4.02	0%	0.52
	total	4	0.61	-3.14 to 4.36	40%	0.17	4	0.31	-3.10 to 3.72	0%	0.71
Bueno 2013 [31]		-	-	-	-	-	11	-1.47	-3.44 to 0.50	33%	0.13

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I^2	p-value for I^2
Hu 2012 [32]	18	-1	-3.5 to 1.5	91.7%	<0.001
Sackner-Bernstein 2015 [33]	NR	-1.7	-3.5 to 0.2	NR	NR
Mansoor 2015 [34]	8	-1.02	-2.98 to 0.94	63.1%	0.008

NR, not reported; DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate

[1] no heterogeneity calculated, only one study.

Table S11. Diastolic blood pressure (mmHg)

Authors		6 months					12 months or more				
		No. of included studies	mean difference	95%CI	I-square	p-value for I-sq	No. of included studies	mean difference	95%CI	I-square	p-value for I-sq
Nordmann 2006 [28]		5	-1.8	-3.7 to 0.1	17%	0.3	3	-0.4	-2.6 to 1.7	1%	0.37
Hession 2009 [29]		6	-0.49	-1.85 to 0.86	10.6%	0.35	4	-0.76	-2.43 to 0.90	1.1%	0.39
Naude 2014 [30]											
No DM	*HF*	6	-0.39	-1.65 to 0.87	34%	0.18	4	0.01	-1.67 to 1.69	3%	0.23
	HP	2	0.85	-5.97 to 7.68	77%	0.04	2	-1.21	-8.89 to 6.48	64%	0.09
	total	8	-0.08	-1.53 to 1.36	51%	0.05	6	0.03	-1.68 to 1.62	29%	0.22
with DM	*HF*	1	-2	-6.02 to 2.02	- [1]	- [1]	1	0.00	-4.82 to 4.82	- [1]	- [1]
	HP	3	1.63	-1.18 to 4.43	32%	0.23	3	0.11	-2.15 to 3.26	0%	0.96
	total	4	0.77	-1.77 to 3.30	39%	0.18	4	0.09	-1.95 to 2.13	0%	0.99
Bueno 2013 [31]		-	-	-	-	-	11	-1.43	-2.49 to -0.37	3%	0.41

Authors	No specific time points (6-24 months)				
	No. of included studies	mean difference	95%CI	I-square	p-value for I-sq
Hu 2012 [32]	18	-0.7	-1.6 to 0.2	0.408	0.04
Mansoor 2015 [34]	8	-1.01	-2.75 to 0.74	77.9%	0.000

DM, diabetes mellitus; HF, high fat/low carbohydrate; HP, high protein/low carbohydrate
[1] no heterogeneity calculated, only one study.

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