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# Carbohydrate quantity in the dietary management of type 2 diabetes – a systematic review and meta-analysis

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## ABSTRACT

*Aims*: This systematic review and meta-analysis compares the effects of low carbohydrate diets (LCDs) on body weight, glycaemic control, lipid profile and blood pressure with those observed on higher carbohydrate diets (HCDs) in adults with type 2 diabetes.

*Methods:* MEDLINE, EMBASE, CENTRAL, CINAHL, Food Science Source and SweMed+ databases were systematically searched to identify randomised controlled trials (duration ≥ 3 months) investigating the effects of a LCD compared to a HCD in the management of type 2 diabetes. Data were extracted and pooled using a random effects model and expressed as mean differences and risk ratio. Subgroup analyses were undertaken to examine the effects of duration of intervention, extent of carbohydrate restriction and risk of bias. The certainty of evidence was assessed using GRADE.

*Results*: Of the 1589 studies identified, 23, including 2178 participants, met inclusion criteria. Reductions were slightly greater on LCDs than HCDs for $HbA_{1c}$ (-1.0 mmol/mol, CI -1.9, -0.1 [-0.09%, CI -0.17, -0.01]) and triglycerides (-0.13 mmol/l, CI -0.24, -0.02). Changes in weight, HDL- and LDL-cholesterol, total cholesterol and blood pressure did not differ significantly between groups. Subgroup analyses suggested that the difference in HbA1c was only evident in studies with duration of ≤6 months and with high risk of bias.

*Conclusions*: The proportion of daily energy provided by carbohydrate intake is not an important determinant of response to dietary management, especially when considering longer term trials. A range of dietary patterns including those traditionally consumed in Mediterranean countries seems suitable for translating nutritional recommendations for people with diabetes into practical advice. Systematic review registration number: CRD42013005825.

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## INTRODUCTION

Dietary advice is generally accepted as a cornerstone of the management of type 2 diabetes (T2DM) [1]. More than 80% of all patients presenting with T2DM are overweight or obese [2,3], and recommendations relating to energy intake and physical activity aimed at weight management are a core component of the treatment of T2DM worldwide [4-7]. However, advice regarding the macronutrient composition has varied over time [8]. With occasional exceptions, carbohydrate restriction was a key component of diabetic dietary prescriptions for much of the 20th Century. In the 1960's it became evident that CHD rates were exceptionally high in people with diabetes and the high fat (predominantly saturated fat) intakes associated with the reduction in carbohydrate were presumed to be a contributory factor. This observation together with the demonstration of the beneficial effects of dietary fibre on glycaemic control and blood lipids in the 1970s led to a change in the nutritional approach. Fibre-rich, low glycaemic index carbohydrates were encouraged and total carbohydrate intake was liberalized in advice to people with diabetes as well as populations at large [4,9-14].

More recent reports, have suggested the potential of appreciable reductions in carbohydrate to facilitate weight reduction and improve glycaemic control, insulin sensitivity, blood pressure, HDL-cholesterol and triglyceride levels to a greater extent than higher carbohydrate diets [15-19]. However, three recent meta-analyses of trials undertaken in people with T2DM reached different conclusions regarding the merits of carbohydrate restriction in this patient group [16,20,21]. In order to inform an update of current European Guidelines for the management and prevention of diabetes, we have undertaken a systematic review and meta-analysis which attempts to circumvent the criticisms which have been levelled at the earlier attempts to aggregate the relevant trials [22,23]. More specifically we wanted to investigate whether a low-carbohydrate diet improved weight and metabolic control more than a higher carbohydrate diet in patients with type 2 diabetes.

## MATERIALS AND METHODS

This systematic review was carried out according to Cochrane recommendations [24], and reported in line with the PRISMA Statement [25] (Supplementary table 1). The protocol for this review was prospectively registered in PROSPERO (CRD42013005825).

### Search strategy and study selection

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Food Science Source and SweMed+ for RCTs published between 1983 to January 2016. Our search terms were: (diet OR carbohydrate-restricted OR low carbohydrate diet OR dietary carbohydrates OR ketogenic diet OR Atkins diet OR diabetic diet) AND (type 2 diabetes OR diabetes mellitus OR type 2 OR diabetes OR non-insulin dependent diabetes mellitus), using MeSH terms when available. We also searched the reference list of identified studies and performed forward citation searches to consider further studies not identified by our online search.

We included randomised controlled trials of parallel or cross-over design with more than three months duration in adults with type 2 diabetes. We had no restrictions regarding minimum number of included subjects. Co-morbidity was accepted, but studies including individuals with impaired glucose tolerance and/or type 1 diabetes were only included whenever separate data for patients with type 2 diabetes were provided. Trials had to compare a diet below to a diet above 40% total energy (E%) from carbohydrate to be included. Complex interventions consisting of elements with the potential to interfere with the effect of the dietary intervention (e.g. parenteral administration or promotion of physical activity) were excluded.

We accepted studies written in English, Danish, Norwegian and Swedish. One review author (HKH) screened all titles and abstracts, and excluded obviously irrelevant records. For the

remaining records, full-text articles were obtained and assessed independently for inclusion by two authors (AMA and HKH). Any disagreements were resolved by consensus.

**Data extraction and risk of bias**

From each study we extracted the name of first author, year of publication, study design, study duration, participant details, intervention diet details, markers of compliance with diets, and the outcomes measured. The following outcomes were considered: weight, $HbA_{1c}$, lipids, blood pressure and compliance to dietary intervention. Data were extracted by one author (HKH), and verified by a second investigator (AMA).

We assessed risk of bias for the main items suggested by Cochrane [24]: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. For each study and outcome, two researchers (HKH and AMA) independently rated the seven domains to low, unclear or high risk of bias.

We applied the following rules to assess the overall risk of bias for each study and outcome:

- Low risk: No high risk of bias, and not more than two unclear risks of bias
- High risk: Two or more high risks of bias, one high and more than one unclear risk, or more than four unclear risks of bias
- The remaining articles were classified as unclear risk of bias

Due to the nature of delivery of dietary interventions, blinding of participants and study personnel that provided dietary advice was not possible. Hence, this item was not considered when assessing the overall risk of bias.

**Data synthesis and analysis**

Results were summarized qualitatively, and whenever applicable, results from available studies were combined in meta-analysis using Review Manager (RevMan) [Computer

program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. We expected clinical heterogeneity among studies, and chose the random-effects model. The weighting of individual trials was defined by inverse variance and mantel-haenszel methods for continuous and dichotomous outcomes, respectively. We calculated the mean difference (MD) for continuous outcomes, whereas dichotomous effect sizes were expressed in terms of a risk ratio (RR). For trials with multiple dietary arms, we pooled data for the higher-carbohydrate diet groups to create one control group [24]. Crossover trials were not included in meta-analysis due to short intervention period and possible carryover effect. The HbA1c unit was converted from % to mmol/mol by the use of a conversion calculator: http://www.ngsp.org/convert2.asp.

Meta-analyses were considered to be associated with heterogeneity when the $I^2$ value was above 50%, and/or the P value of the Cochrane Q test was less than 0.10 [24], and subgroup analysis were used to explore possible reasons for the suggested heterogeneity. In particular, we conducted post-hoc subgroup and sensitivity analyses to explore the impact of study duration (≤6 months vs. ≥12 months), varying carbohydrate content in the LCD-group (very low-carbohydrate diets, VLCD: 21-70 g carbohydrates and moderate LCD: 30-40 E% carbohydrates) [15] and risk of bias (low vs. high).

Two authors (AMA and HKH) independently graded [26] the certainty of the evidence for diets of lower carbohydrate content when compared with diets of higher carbohydrate content in the management of type 2 diabetes. We assessed publication bias for a given outcome by inspection of funnel plots.

## RESULTS

### Search results and characteristics of the included studies

Out of 1589 studies identified through database searches and cross reference list matching, 23 studies were included in the review [27-49] (Fig 1). Main reasons for exclusion were diet intervention not being low-carbohydrate; duration of intervention being less than three months; study sample consisting of individuals without type 2 diabetes and studies using a non-randomised and/ or non-controlled trial design (Supplementary table 2).

The total participant number in the 23 articles was 2178, 1061 participants in the low-carbohydrate group and 1194 participants in the control group. Two studies included participants with and without type 2 diabetes [31,34]. In these studies, only data on the type 2 diabetes participants were extracted. The follow up time ranged from three months [28,29,32,33,38,45,46] to over three years [30]. Studies were published between 1994 [27] and 2014 [46-49]; eight were conducted in North America [27,30,31,33,35-37,46], five in Europe [32,38,42,45,47], five in Australia [28,29,41,44,48], one in New Zealand [43], three in Israel [34,39,40] and one in Japan [49]. Randomised crossover design was used in four studies [27-29,38], and parallel randomised control trials, with one or two control groups, were implemented in 19 studies [30-37,39-49].

A summary of findings from the included studies are presented in Table 1. Twelve studies reported having included individuals who were either overweight or obese [31-35,37,39-41,43,44,48]. Physical activity was not specifically addressed in any of the studies, but several trials promoted general recommendations for physical activity.

The LCD was compared to either low-fat diets [31-34,37,42,47,49], standard diabetes care [38-40,45], high carbohydrate diets [27,29,41], low-protein diets [30,44], a standard protein diet [48], Mediterranean diets [34,39], high carbohydrate, low-fat diets [28,43], a high wheat-fibre diet [46], low-glycaemic index diets [35,36] or a high-glycaemic index diet [36]. The recommended amount of dietary carbohydrates in the low-carbohydrate interventions ranged from five [35] to 40% [27-29,33,41,43-45,48] of the total energy intake. Among the 17 studies that assessed the actual intake of

carbohydrates throughout the study period, all but one [48] found that the difference in carbohydrate intake was statistically significant between the LCD-group and comparator [28,29,32,33,36-43,45-47,49]. In six of the low-carbohydrate interventions [28,29,33,39,47,48], and ten of the comparator diets [28,29,33-35,39,40,47-49] it was intended that participants consumed energy restricted diets that ranged from approximately 5000 kJ (1200 kcal) [40] to 7500 KJ (1800 kcal) [34] per day. Fifteen studies emphasized that weight reduction was a goal of the dietary intervention. Conversely, several trials permitted study participants in the intervention to eat ad libitum while limiting carbohydrate intake.

Mean duration of diabetes among participants varied from one to over 17 years and the participants frequently used medications including insulin therapy [30,31,34,35,37,41-45,47,49], anti-hypertensive drugs [29,30,33,36,38,43,44,46] lipid lowering medications [29,30,33,36-38,42-44,46] and oral hypoglycaemic agents, such as metformin [30,31,35,37,38,42,46-49], sulfonylurea [27,30,31,37,38,42,46-49] and thiazolidinedione [38,46,48,49]. Dietary advice was provided by health professionals, such as dietitians, nutritionists, diet counsellors [29,31,33-37,39-47,49], physicians [42,47] and nurses [42] and incorporated both individual meetings and group sessions.

**Risk of bias in included studies**

Assessment of risk of bias is summarized in supplementary figure 1A and shown for the individual studies in supplementary figure 1B. Method of random sequence generation was reported and found adequate in 15 studies. Eight trials provided sufficient information about the proceedings of allocation concealment and they were rated as low risk. As expected, few studies blinded study participants and personnel to the dietary interventions (with the exception of one trial [40]), and were thus rated as unclear risk of bias. Five studies reported blinding of outcome assessors. Furthermore, one study [29] had high risk of attrition bias due to incomplete reporting of outcome data, as only compliers were incorporated in analysis and non-adhering participants were excluded. Selective reporting was found in four trials. Overall,

when using the predefined criteria, the study level assessment showed that ten trials had high risk of bias [27-32,35,45,47,49], three had low risk of bias [41,43,48] and the remaining ten studies were considered as unclear risk of bias [33,34,36-40,42,44,46], (Supplementary figure 1). The Funnel plots for the different outcomes did not indicate any publication bias (Supplementary figure 2).

**Body weight**

Of the 20 studies that incorporated changes in body weight as an outcome, 17 provided sufficient information to be included in the meta-analysis, comprising 739 participants randomised to the LCD and 848 randomised to the HCD. Overall, LCD was not associated with greater weight loss than HCD in either short or long term studies (Figure 2A), but subgroup analysis suggested more positive results in short term studies (≤ 6 months) than in studies with longer follow up (Supplementary table 3a). Sensitivity analysis showed less difference between LCD and HCD in studies with low risk of bias than in studies with high risk of bias (supplementary table 3C). In the three cross-over studies of 3 months duration [28,29,38] which did not fulfill criteria for inclusion in the meta-analysis, one [38] showed greater weight loss associated with LCDs. The certainty of evidence was moderate, with little heterogeneity ($I^2$ = 29%), (Supplementary table 4).

**Glycaemic control**

LCD was associated with a greater overall reduction in $HbA_{1c}$ (MD -1.0 mmol/mol, 95% CI -1.9, -0.1 [-0.09 %, 95% CI -0.17, -0.01]) in the 16 studies included in this analysis. This result is largely driven by the results of the short term studies (Figure 2B, Supplementary table 3a), and by trials associated with high risk of bias (Supplementary table 3C). Of the three further short term studies not included in the meta-analysis [28,29,38] one [38] showed greater improvements on LCDs. The evidence was considered as having moderate certainty for this outcome (Supplementary table 4).

**Serum lipids and blood pressure**

Sixteen RCTs are included in the pooled analyses of the effects on HDL-cholesterol and Triglycerides, 15 studies in the analysis of LDL-cholesterol and 14 in the analysis of total cholesterol. The meta-analyses showed no significant difference between groups in effect on HDL-cholesterol (MD 0.04 mmol/l, 95% CI -0.01, 0.10; low evidence), LDL-cholesterol (MD -0.01 mmol/l, 95% CI -0.13, 0.11; low evidence), and total cholesterol (MD 0.04 mmol/l, 95% CI -0.12, 0.20; low evidence), but a slightly greater reduction in triglycerides with LCD (MD -0.13, 95% CI -0.24, -0.02 mmol/l; low evidence), (Figure 3D, Supplementary table 4). There was evidence for considerable between-study heterogeneity for triglycerides ($I^2$ = 57%, $p < 0.003$), HDL-cholesterol ($I^2$ = 72%, $p < 0.0001$), LDL-cholesterol ($I^2$ = 64%, p = 0.0004) and total cholesterol ($I^2$ = 71%, $p < 0.0001$).

The reasons for the observed heterogeneity were explored in subgroup and sensitivity analysis. No consistent subgroup effects were observed across the three outcomes, even though HDL-cholesterol was slightly higher on LCD than HCD in long term studies (p=0.10, Figure 3B, Supplementary table 3A) and LDL-cholesterol was higher in VLCD-trials compared with moderate LCD (p=0.05, Supplementary table 3B and Supplementary figure 3). Trials with low risk of bias showed less difference between LCD and HCD for changes in HDL-cholesterol and triglyceride than trials associated with high risk of bias, whereas the results were more consistent for LDL- and total cholesterol.

Sixteen trials examined the effect of a LCD on blood pressure. As shown in Figure 4A and B, the pooled effect from the meta-analysis indicated no significant difference in effect of the LCD on systolic (SBP) and diastolic blood pressure (DBP) when compared to control (SBP: MD -0.93 mmHg, 95% CI -2.24, 0.37, DBP: MD -0.21 mmHg, 95% CI -1.20, 0.79). Two of the three studies that were not included in the meta-analyses showed a greater reduction in

DBP in the LCD group [36,38]. The certainty of evidence was considered low for both outcomes due to risk of bias and imprecision (Supplementary table 4). No evidence of between study heterogeneity was identified in the meta-analyses ($I^2$ = 0%).

**Compliance and attrition rate**

By using 24-hour recalls or food records, nine out of 18 studies found that dietary intake of carbohydrates in the LCD were 5 E% within what was recommended. In seven out of nine trials that observed low compliance, participants were on VLCD with 5 to 22 E% from carbohydrates [31,32,34,35,37,40,42]. Four of these studies were based on an Atkins diet [34,35,37,40]. In the meta-analysis of attrition rates between LCD and HCD, no detectable difference in attrition was observed: RR 1.08 (95% CI 0.92, 1.27; $I^2$ = 0%), (Figure 4C). The results were similar in trials associated with high and low risk of bias. The certainty of evidence for attrition was downgraded to low due to risk of bias and imprecision (Supplementary table 4).

**Carbohydrate and fat quality in the diets**

Seven of the included studies gave no information regarding dietary intake or only information on macronutrient distribution. Sixteen studies assessed dietary intake and 15 of these reported information regarding the nature of carbohydrate eaten (fibre, Glycemic Index or load, sucrose, key foods provided in feeding trials). In 9/15 trials the intake of fibre was higher in the HCD, while six trials reported no differences in fibre intake. GI /GL were higher in the HCD in the two studies that reported this, while the intake of sucrose was lower in the LCD in one of the three trials that reported sucrose intake. In seven of the trials unsaturated fatty acids substituted carbohydrates in the LCDs. This resulted in a significantly higher intake of unsaturated fatty acids in the LCD compared with the HCD in six of the trials that reported fatty acid composition while intake of saturated fat increased only in two of these studies

## DISCUSSION

This systematic review and meta-analysis shows that the minimally lower levels of $HbA_{1c}$ apparent when comparing diets with very low (21 – 70g) or low (30 to 40 E%) carbohydrate content with those providing a higher carbohydrate content (greater than 40 E%) are driven by trials with a duration of six months or less and by trials associated with high risk of bias. The only consistent difference between the studies with higher and lower carbohydrate intakes was a small difference (0.13mmol/l) in triglyceride levels, but this was also most evident in trials with high risk of bias. No differences in weight, blood pressure or total, LDL and HDL cholesterol were apparent in either the relatively short or longer term trials.

Our systematic review and meta-analysis identified all relevant trials published between 1983 and January 2016 and therefore included an appreciably greater number of studies than earlier meta-analyses, thus enabling more convincing conclusions than previously possible. Other strengths included strict compliance with the established criteria for the conduct of such a review and meta-analysis, including registration and specification of methodology prior to the literature search, the involvement of two researchers to independently extract and assess the trials, and the use of GRADE methodology to evaluate the certainty of the evidence. The inevitable limitation of any such review stems from the quality of the included trials and the extent to which participants achieved adherence to prescribed diets, which in studies of free living individuals inevitably diminishes over time. The observation that trials with high risk of bias are associated with more favourable results for the LCD in many analysis highlights a potential pitfall in the interpretation of individual studies, meta-analysis and subgroup analysis. We attempted to assess compliance with prescribed diets and determine the extent to which nature of carbohydrate might have influenced outcome. While there appeared to be a relatively high level of compliance with the LCD, it was evident that the ability to follow a

diet with *very* low-carbohydrate content was generally poor. Furthermore, changes in medications over time may have blurred effects of differences in diet composition. The limited information given in the included studies suggests that particularly the very low-carbohydrate diet groups had a greater reduction in the use of diabetes medication (mainly insulin) that may have masked a more positive impact on glycaemic control than what we have shown. On the other hand, only four studies showed a significant difference in change in diabetes medication between the diets and some of the studies repeated their analyses adjusting for difference in medication and found that it did not alter the conclusions.

Ajala et al [16] reported a review and meta-analysis which examined the effects of low-carbohydrate, low-GI, high-fibre, high-protein, Mediterranean, vegetarian and vegan diets compared with control diets in trials continued for six months or more. They reported a range of benefits including an improvement in glycaemic control associated with all these dietary patterns and concluded that they were appropriate for people with diabetes. However given that neither the low carbohydrate nor the comparator diets were clearly defined, it is not possible to disentangle the effect of carbohydrate quantity from other dietary attributes on the various outcome measures. Our meta-analysis also included trials with a range of carbohydrate intakes, but differences between low and higher intakes were clearly specified and we used a random effects analysis, rather than a fixed effect analysis (as performed by Ajala and colleagues [16]) to take into account the heterogeneity of studies. Naude et al [20], on the other hand, concluded that there were no differences in either body weight or glycaemic control when altering carbohydrate quantity, but their meta-analysis included only five trials which involved isoenergetic comparisons, thus limiting any chance of finding differences in weight change or glycaemic control as a consequence of altering macronutrient distribution.

In a more recently published systematic review and meta-analysis, Snorgaard et al [21], like us concluded that the modestly beneficial effect on glycaemia conferred by low carbohydrate

diets was only apparent in the short term. However, our analysis differed from their approach in that we considered the outcomes of the relatively short and longer term trials separately, whereas five of the eight studies providing 3-6 month data in the Snorgaard et al review were also the source of the 12 month data. They also reported that the effect on glycaemic control was related to the extent of carbohydrate restriction. This association was totally dependent upon the findings of two trials [50,51] of 3 months duration that were not included in our analyses because they included subjects with prediabetes [50] or implemented an additional physical activity intervention [51]. When examining the forest plots for VLCD diets and moderate LCD diets separately there appeared to be a better effect of VLCD on $HbA_{1c}$ also in our meta-analysis, but post hoc subgroup analysis did not confirm this. On the contrary, the subgroup analysis showed that VLCD had a less favourable effect on LDL-cholesterol compared with HCD while this difference was not shown in studies using moderate LCD. The period of Snorgaard et al's [21] search (2004 – 2014) was appreciably shorter than the period covered by the present study and the upper cut-off used to define low carbohydrate diets was 45 E% whereas we chose the somewhat lower cut-off, 40 E% .

Short term benefits of low and very low carbohydrate diets in terms of weight loss and improvements in blood pressure and blood lipid profile have also been shown in normoglycaemic individuals [18,19]. It has not been possible to disentangle whether the short term improvement in glycaemic control and a range of cardiovascular risk factors is a consequence of the weight loss or a direct result of carbohydrate restriction and/or the consequential redistribution of the proportion of energy provided by other macronutrients. It is also uncertain whether the failure to demonstrate meaningful long term benefits results from failure to comply with advice to reduce carbohydrate or a consequence of adaptation to an altered dietary pattern. Nevertheless it is clearly the longer term outcome data which are of relevance to the practical application of these findings.

Several issues need to be taken into account when translating these findings into nutritional advice for people with type 2 diabetes. Weight reduction was a goal in the majority of the studies and the improvements seen on lower carbohydrate diets were mainly observed when weight loss was achieved. Thus it is unclear whether the patient would benefit from carbohydrate reduction if weight loss is not achieved. Advice regarding the proportion of total energy provided by carbohydrate also needs to take into account the source and nature of carbohydrate and the effects of the other macronutrients. A substantial number of studies mainly carried out in the 1980s and 1990s demonstrated benefit in terms of glycaemic control and cardiovascular risk factors in association with relatively high carbohydrate diets rich in dietary fibre derived from legumes, vegetables and fruit [4]. Of particular relevance to the interpretation of the results of the present analysis, is that triglyceride levels were not increased even when carbohydrate intakes were high (around 60 E%) in these earlier studies provided that much of the carbohydrate was derived from sources rich in dietary fibre and slowly digested starches. Altered intakes of fat and protein resulting from changing the proportion of energy from carbohydrate may also influence glycaemic control and indicators of cardiovascular risk. Many of the LCD interventions included in our meta-analysis promoted increased intake of unsaturated fat but not saturated fat. Thus the findings have no direct bearing on several widely promoted low carbohydrate high fat diets in which saturated fat is not restricted or may even be encouraged. Detailed dietary data was not provided in many of the studies included in the meta-analysis so it is not possible at present to disentangle the effects of carbohydrate quantity from carbohydrate quality and other macronutrients. Finally, of the 13 studies that reported on the incidence of adverse effects only one [30] reported worse outcome on indicators of nephropathy with the HCD. The rest of the trials reported no serious or important adverse events and no difference between groups in reported mild adverse effects such as mild hypoglycaemia.

Further long term dietary intervention studies taking into account both amount and source of carbohydrate would be helpful in refining nutritional recommendations for people with diabetes. However, in practice nutrition recommendations require translation into dietary patterns in order for them to be implemented. On the basis of currently available systematic reviews and meta-analyses there is an appreciable body of evidence to suggest that a traditional Mediterranean type diet is particularly appropriate for people with T2DM [16, 52-54]. Mediterranean diets vary in the proportion of energy provided by macronutrients but are typically rich in pulses, fruits, vegetables, and nuts with olive oil being a major contributor to fat intake. Other dietary approaches including a healthy Nordic diet and vegetarian diets may also be beneficial for people with diabetes [16, 52, 54-59]. None of these dietary patterns is particularly low or high in carbohydrate. The range of possibilities enhances the concept of personal preference playing a key role in the prescription of dietary advice as well as permitting appreciable restriction of rapidly digested starches and sugars for those with insulin resistance. While energy balance remains a cornerstone of all dietary advice for people with diabetes, the proportion of macronutrients seems to be less important.

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## Figure legends

**Figure 1** PRISMA Study eligibility flow chart

**Figure 2** Meta-analysis of changes in body weight (kg) [A] and HbA1c (%) [B] divided according to study duration

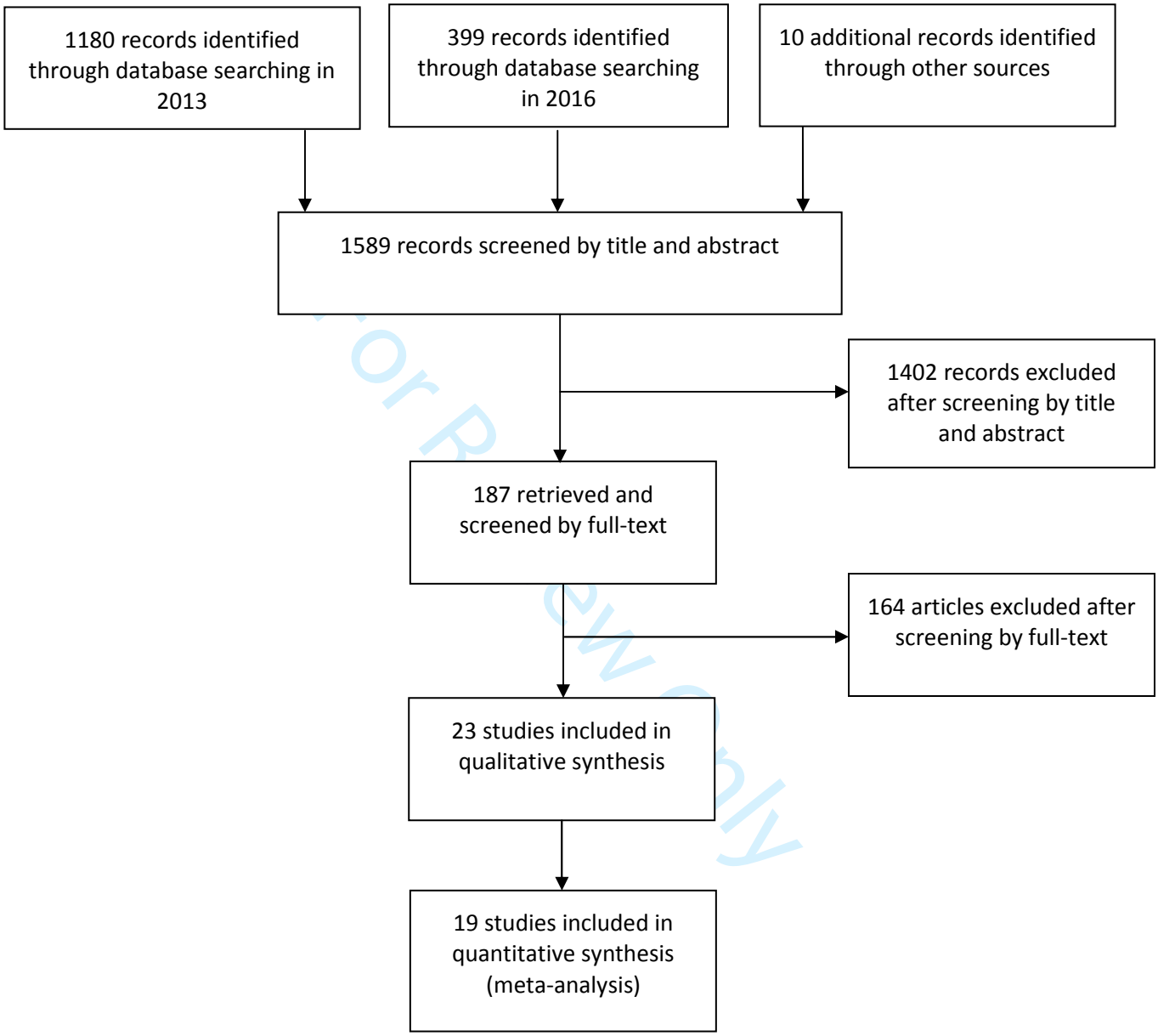
**Figure 3** Meta-analysis of changes in LDL-cholesterol[A], HDL-cholesterol [B], Total cholesterol [C] and Triacylglyserols [D], all measured in mmol/l, divided according to study duration

**Figure 4** Meta-analysis of Systolic [A] and Diastolic blood pressure (mmHg) [B] and Attrition rate(Risk ratio) [C] divided according to study duration

## Supplementary Appendix:

- Supplementary table 1: PRISMA Checklist for preferred reporting items in systematic reviews and Meta-Analyses
- Supplementary table 2: List of excluded studies
- Supplementary table 3
    - A) Subgroup-analysis based on study duration ≤6 months (short term) vs ≥12 moths (long term)
    - B) Subgroup-analysis based on the amount of carbohydrates in the LCD group, LCD (21-70 g CHO) vs LCD (30-40% TE CHO)
    - C) Sensitivity-analysis based on high versus low risk of bias
- Supplementary table 4: Summary of findings across studies

- Supplementary figure 1: Risk of bias graphs.
  - A) Summary of the internal validity of the included studies
  - B) Summary for the individual RCTs
- Supplementary figure 2: Funnel plots for the individual outcomes
- Supplementary figure 3: Forest plots divided according to carbohydrate restriction in the LCD group



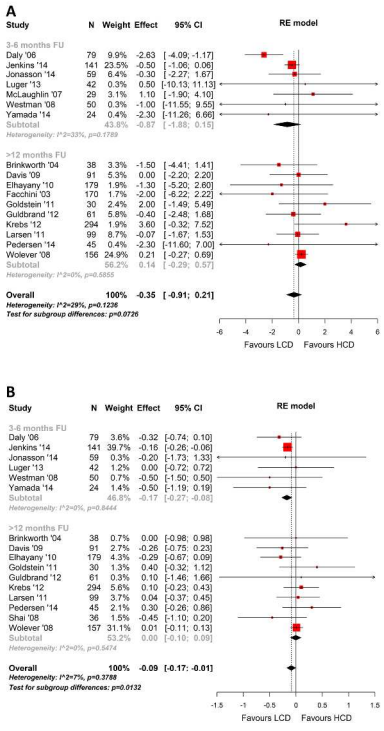



Figure 2 Meta-analysis of changes in body weight (kg) [A] and HbA1c (%) [B] divided according to study duration

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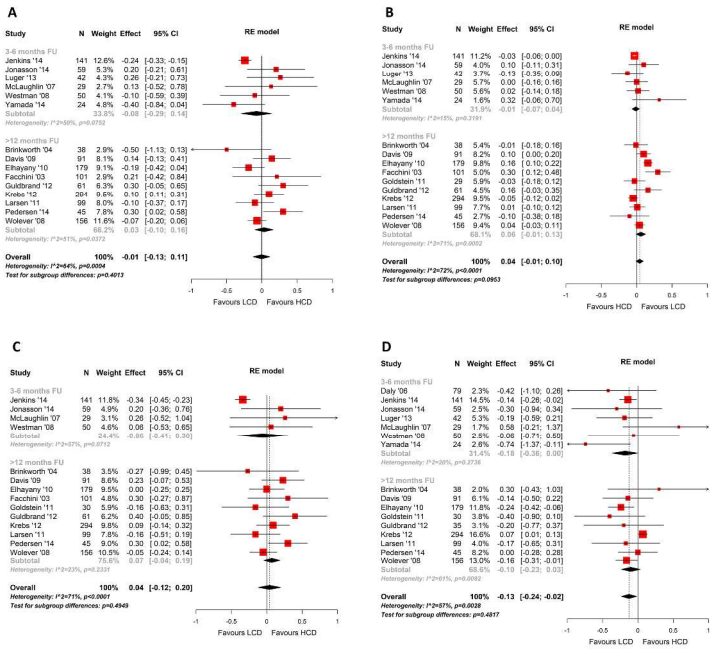


Figure 3 Meta-analysis of changes in LDL-cholesterol[A], HDL-cholesterol [B], Total cholesterol [C] and Triacylglyserols [D], all measured in mmol/l, divided according to study duration

275x397mm (300 x 300 DPI)

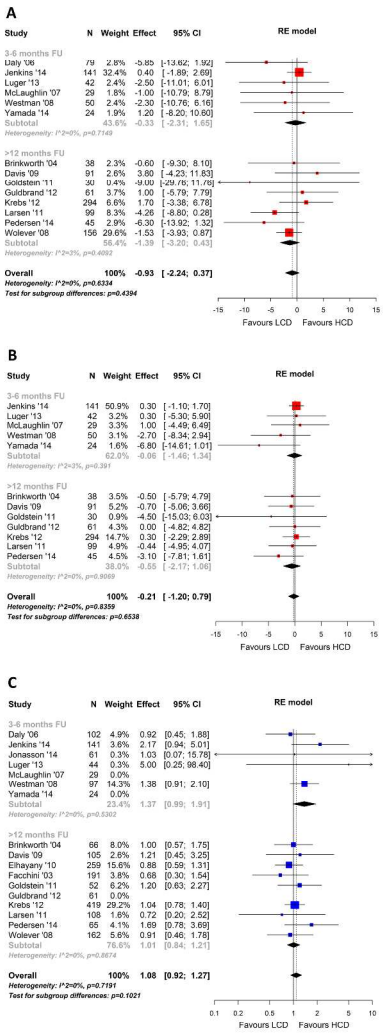


Figure 4 Meta-analysis of Systolic [A] and Diastolic blood pressure (mmHg) [B] and Attrition rate (Risk ratio) [C] divided according to study duration

275x397mm (300 x 300 DPI)

**Table 1** Characteristics and summary of findings of studies selected for inclusion in the review. Outcomes show significant findings within the low-carbohydrate group, and between dietary groups

| Study details | Study design | Participants randomized | LCD | Comparator | Outcome | Duration | Weight | HbA1c | Serum lipids | Blood pressure | Compliance to LCD – Presented as mean±SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **MODERATE LOW-CARBOHYDRATE DIETS** | | | | | | | | | | | |
| **Brinkworth et al., [44] Australia (2004)** | Randomised controlled trial | 66 obese type 2 diabetes patients | 40 E% CH<br>30 E% fat<br>30 E% protein | 55 E% CH<br>30 E% fat<br>15 E% protein | Weight<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by attrition[a] | 16 months | Weight reduced (p<0.01). No difference between groups | NS | HDL increased (p<0.001). No difference between groups | DBP reduced (p<0.05). Greater reduction in SBP and DBP with the LCD (p=0.04 and <0.008)[b] | NA |
| **Elhayany et al., [39] Israel (2010)[c]** | Randomised controlled trial | 259 overweight type 2 diabetes patients | 35 E% CH<br>45 E% fat<br>15-20 E% protein | 50-55 E% CH<br>30 E% fat<br>20 E% protein | Weight,<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Compliance by food records and attrition | 12 months | Weight reduced (p<0.001). No difference between groups | HbA1c reduced (p<0.001). Greater reduction with the LCD (p=0.021) [d, e] | LDL, HDL, TG and TC improved (p<0.001). Greater improvements in LDL[d], HDL[d e] and TG[d] with the LCD (p=0.036, <0.001 and <0.001) | NA | 42 E% CH |
| **Facchini et al., [30] USA (2003)** | Randomised control trial | 191 type 2 diabetes patients with renal failure | 35 E% CH<br>30 E% fat<br>25-30 E% protein<br>5-10 E% ethanol | 65 E% CH<br>25 E% fat<br>10 E% protein | Weight<br>HbA1c<br>LDL, HDL, TC | Mean follow-up 3.0±1.8 years | NS | NS | HDL increased [f]<br>No difference between groups | NA | NA |
| **Garg et al., [27] USA (1994)** | Randomised crossover trial | 21 type 2 diabetes patients | 40 E% CH<br>45 E% fat<br>15 E% protein | 55 E% CH<br>30 E% fat<br>15 E% protein | LDL, HDL<br>TG, TC | 14 weeks | NA | NA | TG reduced (p=0.03). No difference between groups | NA | NA |
| **Jenkins et al., [46] Canada (2014)** | Randomised controlled trial | 141 type 2 diabetes patients | 39 E% CH [g]<br>37 E% fat [g]<br>20 E% protein[g] | 49 E% CH [g]<br>27 E% fat [g]<br>20 E% protein [g] | Weight<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by attrition | 3 months | Weight reduced (p<0.05). No difference between groups | HbA1c reduced (p<0.05). No difference between groups | LDL, HDL, TG and TC reduced (p<0.05). Greater reduction in LDL, HDL, TC and TG with the LCD (p<0.01, =0.04, <0.01 and =0.18) | SBP and DBP reduced (p<0.05). No difference between groups | Not applicable [g] |
| **Jönsson et al., [38] Sweden (2009)** | Randomised crossover trial | 13 non-insulin treated type 2 diabetes patients | 32 E% CH<br>39 E% fat<br>24 E% protein | 42 E% CH<br>34 E% fat<br>20 E% protein | Weight,<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records | 3 months | Weight reduced (p=0.005 and 0.01). Greater reduction in weight with the LCD (p=0.01 and 0.04) | HbA1c reduced (p<0.001). Greater reduction with the LCD (p=0.02) | TG reduced (p=0.003). Greater improvements in HDL and TG with the LCD (p=0.03 and 0.003) | SBP reduced (p=0.048). Greater reduction in DBP with the LCD (p=0.03) | 32±7 E% CH<br>39±5 E% fat<br>24±3 E% protein |
| **Krebs et al., [43]** | Randomised | 419 overweight | 40 E% CH | 55 E% CH | Weight | 24 months | Weight reduced | NS[f] | NS[f] | NS | 46±7 E% CH |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **New Zealand (2012)** | controlled trial | type 2 diabetes patients | 30 E% fat<br>30 E% protein | 30 E% fat<br>15 E% protein | HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records and attrition | | (p<0.001). No difference between groups | | | | 33±6 E% fat<br>21±4 E% protein |
| **Larsen et al., [41] Australia (2011)** | Randomised controlled trial | 108 overweight and obese type 2 diabetes patients | 40 E% CH<br>30 E% Fat<br>30 E% Protein | 55 E% CH<br>30 E% Fat<br>15 E% Protein | Weight<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records and attrition | 12 months | Weight reduced (p<0.001). No difference between groups | HbA1c reduced (p<0.001).<br>No difference between groups | HDL and TG improved[f].<br>No difference between groups | NS[f] | 42 E% CH<br>31 E% fat<br>27 E% protein |
| **Luger et al., [45] Austria (2013)** | Randomised controlled trial | 44 insulin treated type 2 diabetes patients | 40 E% CH<br>30 E% fat<br>30 E% protein | 55 E% CH<br>30 E% fat<br>15 %% protein | Weight<br>HbA1c<br>LDL, HDL, TG<br>Blood pressure<br>Compliance by food records and attrition | 3 months | Weight reduced (p<0.001). No difference between groups | HbA1c reduced (p=0.05). No difference between groups | TG reduced (p=0.01). No difference between groups | DBP reduced (p=0.005). No difference between groups | 38±7 E% CH<br>35±6 E% fat<br>26±5 E% protein |
| **McLaughlin et al., [33] USA (2007)** | Randomised controlled trial | 29 overweight, diet-treated type 2 diabetes patients | 40 E% CH<br>45 E% fat<br>15 E% protein | 60 E% CH<br>25 E% fat<br>15 E% protein | Weight<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records and attrition | 3 months | Weight reduced (p<0.001). No difference between groups | NA | TG reduced (p=0.008). No difference between groups | NS | 43 E% CH<br>38 E% fat<br>19 E% protein |
| **Pedersen et al., [48] Australia (2014)** | Randomised controlled trial | 76 overweight type 2 diabetes patients | 40 E% CH<br>30 E% fat<br>30 E% protein | 50 E% CH<br>30 E% fat<br>20 E% protein | Weight,<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by attrition | 12 months | Weight reduced (p<0.001). No difference between groups | HbA1c reduced (p=0.01). No difference between groups | HDL and TG improved (p<0.01 and <0.001). Greater increase in LDL with the LCD (p=0.05) | Greater reduction in DBP with the LCD (p=0.01) | 197±16 g CH (40 E%)<br>78±7 g fat (35 E%)<br>131±10 g protein (26 E%) |
| **Walker et al., [28] Australia (1995)** | Randomised crossover trial | 24 type 2 diabetes patients | 40 E% CH<br>40 E% fat | 59 E% CH<br>21 E% fat | Weight, HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records | 3 months | Weight reduced (p<0.005). No difference between groups | NS | NS | NS | 40±1 E% CH<br>36±1 E% fat<br>22±1 E% protein |
| **Walker et al., [29] Australia (1999)** | Randomised crossover trial | 34 post-menopausal women with type 2 diabetes | 40 E% CH<br>40 E% fat | 60 E% CH<br>20 E% fat | Weight<br>HbA1c<br>HDL, TG, TC<br>Compliance by food records | 3 months | Weight reduced (p<0.01). No difference between groups | NS[h] | NS[h] | NA | 43±5 E% CH<br>33±5 E% fat<br>21±2 E% protein |
| **Wolever et al., [36] Canada (2008)** | Randomised controlled trial | 162 diet-treated type 2 diabetes patients | 39 E% CH[g]<br>40 E% fat[g]<br>19 E% protein[g] | 47 E% CH[g]<br>31 E% fat[g]<br>20 E% protein[g]<br><br>52 E% CH[g]<br>27 E% fat[g]<br>21 E% protein[g] | Weight<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by attrition | 12 months | Weight reduced (p=0.003). No difference between groups | HbA1c increased (p<0.0001).<br>No difference between groups | LDL reduced (p=0.0079). No difference between groups | DBP reduced (p=0.0080). Greater reduction in DBP with the LCD (p=0.020) | Not applicable[g] |
| **Yamada et al., [49] Japan (2014)** | Randomised controlled trial | 24 type 2 diabetes patients | <130-70 g/day CH (33 E%) | 50-60 E% CH<br><25 E% fat | Weight,<br>HbA1c | 6 months | NS | HbA1c reduced (p=0.03). Greater | TG reduced (p=0.02). No | NS | 30±13 E% CH<br>45±9 E% fat |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | <20 E% protein | LDL, HDL, TG<br>Blood pressure<br>Compliance by food records and attrition | | | reduction with the LCD (p=0.03) | difference between groups | | 25±7 E% protein |
| **VERY LOW-CARBOHYDRATE DIETS** | | | | | | | | | | | |
| **Daly et al., [32] UK (2006)** | Randomised controlled trial | 102 obese patients with poorly controlled type 2 diabetes | < 70 g/d CH (22 E%)<br>No information provided on intake of fat and protein | 45 E% CH[g]<br>33 E% fat[g]<br>21 E% protein[g] | Weight<br>HbA1c<br>TG<br>SBP<br>Compliance by food records and attrition | 3 months | Greater reduction in weight with the LCD (p=0.001) | No difference between groups | No difference between groups | No difference between groups | 34 E% CH<br>40 E% fat<br>26 E% protein |
| **Davis et al., [37] USA (2009)** | Randomised controlled trial | 105 overweight type 2 diabetes patients | 20-25 g/d CH (5-6 E%) for two weeks, then a 5 g increase each week | 50 E% CH[g]<br>25 E% fat<br>19 E% protein[g] | Weight<br>HbA1c1<br>LDL, HDL, TG, TC<br>Blood pressure<br>Compliance by food records and attrition | 12 months | NS[f] | NS[f] | Greater increase in HDL with the LCD (p=0.002). | NS[f] | 33±13 E% CH<br>44±11 E% fat<br>23±7 E% protein |
| **Goldstein et al., [40] Israel (2011)** | Randomised controlled trial | 56 obese type 2 diabetes patients | <25 g/d CH (<6 E%) for 6 weeks, then <40 g/d (<10 E%)<br>No restrictions on intake of fat and protein | 80 E% divided between CH and fats<br>10-20 E% protein | Weight<br>HbA1c<br>HDL, TG, TC<br>Blood pressure<br>Compliance by food records and attrition | 12 months | Weight reduced (p<0.001). No difference between groups | Reduction in HbA1c[f]<br>No difference between groups | NS | NS | 85±35 g CH (20 E%)<br>111±45 g fat (58 E%)<br>102±37 g protein (24 E%) |
| **Guldbrand et al., [42] Sweden (2012)** | Randomised controlled trial | 61 type 2 diabetes patients | 20 E% CH<br>50 E% fat<br>30 E% protein | 55-60 E% CH<br>30 E% fat<br>10-15 E% protein | Weight,<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records and attrition | 24 months | Weight reduced (p=0.020 and 0.011). No difference between groups | NS | LDL and HDL improved (p=0.020 and <0.001). No difference between groups | SBP and DBP reduced (p=0.012 and 0.004).<br>No difference between groups | 31±6 E% CH<br>44±5 E% fat<br>24±4 E% protein |
| **Jonasson et al., [47] Sweden (2014)** | Randomised controlled trial | 61 type 2 diabetes patients | 20 E% CH<br>50 E% fat<br>30 E% protein | 55-60 CH<br>30 E% fat<br>10-15 E% protein | Weight[f], HbA1c<br>LDL, HDL<br>TG, TC<br>Compliance by food records and attrition | 6 months | Weight reduced[f].<br>No difference between groups | HbA1c reduced (p<0.01). No difference between groups | HDL increased (p<0.05). No difference between groups | NA | 25±8 E% CH<br>49±8 E% fat<br>23±4 E% protein |
| **Samaha et al., [31] USA (2003)** | Randomised controlled trial | 52 severely obese type 2 diabetes patients | <30 g/d CH (8 E%)<br>No restrictions on intake of fat | 51 E% CH[g]<br>30 E% fat<br>16 E% protein[g] | HbA1c<br>Compliance by food records[i] | 6 months | NA | NS[f] | NA | NA | 37±18 E% CH<br>41±16 E% fat<br>22±9 E% protein |
| **Shai et al., [34] Israel (2008)** | Randomised controlled trial | 46 moderately obese type 2 diabetes patients | 20 g/d CH (6 E%) for two months, then max 120 g/d (34 E%)<br>No restrictions on intake of fat and protein | 51 E% CH[g]<br>30 E% fat<br>19 E% protein[g]<br><br>50 E% CH[g]<br>35 E% fat<br>19 E% protein[g] | HbA1c<br>Compliance by food records[i] | 24 moths | NA | Hba1c reduced (p<0.05).<br>No difference between groups | NA | NA | 40±7 E% CH<br>39±5 E% fat<br>22±4 E% protein |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| **Westman et al., [35] USA (2008)** | Randomised controlled trial | 84 obese type 2 diabetes patients | < 20 g/d CH (5 E%)<br>No information provided on intake of fat and protein | 55 E% CH[g]<br>36 E% fat<br>20 E% protein[g] | Weight,<br>HbA1c<br>LDL, HDL<br>TG, TC<br>Blood pressure<br>Compliance by food records and attrition | 6 months | Weight reduced ($p<0.05$). Greater reduction in weight and BMI with the LCD ($p=0.008$ and 0.05) | HbA1c reduced ($p=0.009$). Greater reduction with the LCD ($p=0.03$) | HDL and TG improved ($p<0.05$). Greater increase in HDL with the LCD ($p<0.001$) | SBP and DBP reduced ($p<0.05$). No difference between groups | 13 E% CH<br>59 E% fat<br>28 E% protein |

LCD, low-carbohydrate diet; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triacylglycerol; TC, total cholesterol; E%, percent of energy from macronutrient; CH, carbohydrate; NS, not significant; N/A, not assessed

[a] Compliance measured at three months

[b] P value represent between groups change from week 12 to 64

[c] Two control groups with the same macronutrient composition (American Diabetic Association (ADA) vs. Traditional Mediterranean Diet (TMD)

[d] LCD significantly improved compared to ADA

[e] LCD significantly improved compared to TM

[f] p-value on effect within diet group not provided

[g] Macronutrient value shows the actual intake during study/end of study

[h] P value on effect between groups not provided, but the authors state that no difference was seen between the two diets; no information available on within-group effect

[i] Data on macronutrient intake during study was extracted from the whole study population

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 6-7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6-7 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6-7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8, fig. 1, ESM table 2 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9-12 (reported in text per outcome), ESM fig. 1, ESM table 4 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Fig. 2-4 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Fig. 2-4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 9-10, ESM table 4, ESM fig 2 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 10-11 (reported in text per outcome), ESM table 3, ESM Fig |

# PRISMA 2009 Checklist

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| | | | 3 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 16 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13-17 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 17 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

**Supplementary table 2: List of excluded studies (assessed by full-text)**

| Study | | Reason for exclusion |
|---|---|---|
| 1. | Albarran NB, Ballesteros MN, Morales GG, Ortega MI. Dietary behavior and type 2 diabetes care. *Patient Education And Counseling.* 2006;61(2):191-199. | Did not address the main objective of the study |
| 2. | Al-Shookri A, Khor GL, Chan YM, Loke SC, Al-Maskari M. Effectiveness of medical nutrition treatment delivered by dietitians on glycaemic outcomes and lipid profiles of Arab, Omani patients with Type 2 diabetes. *Diabetic Medicine: A Journal Of The British Diabetic Association.* 2012;29(2):236-244. | Did not address the main objective of the study |
| 3. | Andersén E, Hellström P, Kindstedt K, Hellström K. Effects of a high-protein and low-fat diet vs a low-protein and high-fat diet on blood glucose, serum lipoproteins, and cholesterol metabolism in noninsulin-dependent diabetics. *The American Journal Of Clinical Nutrition.* 1987;45(2):406-413. | Participants in the control-group consisted of individuals without type 2 diabetes |
| 4. | Andrews RC, Cooper AR, Montgomery AA, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. *Lancet.* 2011;378(9786):129-139. | Diet intervention not low-carbohydrate; Physical activity advice provided |
| 5. | Ash S, Reeves MM, Yeo S, Morrison G, Carey D, Capra S. Effect of intensive dietetic interventions on weight and glycaemic control in overweight men with Type II diabetes: a randomised trial. *International Journal Of Obesity And Related Metabolic Disorders: Journal Of The International Association For The Study Of Obesity.* 2003;27(7):797-802. | Diet intervention not low-carbohydrate |
| 6. | Azadbakht L, Fard NRP, Karimi M, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. *Diabetes care.* 2011;34(1):55-57. | Duration less than 3 moths |
| 7. | Barakatun Nisak MY, Ruzita AT, Norimah AK, Gilbertson H, Nor Azmi K. Improvement of dietary quality with the aid of a low glycemic index diet in Asian patients with type 2 diabetes mellitus. *Journal Of The American* | Diet intervention not low-carbohydrate |

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| | *College Of Nutrition.* 2010;29(3):161-170. | |
| 8. | Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care.* 2006;29(8):1777-1783. | Diet intervention not low-carbohydrate |
| 9. | Barnard ND, Cohen J, Jenkins DJA, et al. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. *The American Journal Of Clinical Nutrition.* 2009;89(5):1588S-1596S. | Diet intervention not low-carbohydrate |
| 10. | Barnard ND, Gloede L, Cohen J, et al. A low-fat vegan diet elicits greater macronutrient changes, but is comparable in adherence and acceptability, compared with a more conventional diabetes diet among individuals with type 2 diabetes. *Journal Of The American Dietetic Association.* 2009;109(2):263-272. | Diet intervention not low-carbohydrate |
| 11. | Beattie VA, Edwards CA, Hosker JP, Cullen DR, Ward JD, Read NW. Does adding fibre to a low energy, high carbohydrate, low fat diet confer any benefit to the management of newly diagnosed overweight type II diabetics? *British Medical Journal (Clinical Research Ed).* 1988;296(6630):1147-1149. | Diet intervention not low-carbohydrate |
| 12. | Ben-Avraham S, Harman-Boehm I, Schwarzfuchs D, Shai I. Dietary strategies for patients with type 2 diabetes in the era of multi-approaches; review and results from the Dietary Intervention Randomized Controlled Trial (DIRECT). *Diabetes Research And Clinical Practice.* 2009;86 Suppl 1:S41-S48. | The DIRECT-trial is included in the review, but with another publication |
| 13. | Blaak EE, Glatz JF, Saris WH. Increase in skeletal muscle fatty acid binding protein (FABPC) content is directly related to weight loss and to changes in fat oxidation following a very low calorie diet. *Diabetologia.* 2001;44(11):2013-2017. | Did not address the main objective of the study |
| 14. | Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Annals Of Internal Medicine.* 2005;142(6):403-411. | Duration less than 3 moths |

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|---|---|---|
| 15. | Booth FW, Chakravarthy MV. Physical activity and dietary intervention for chronic diseases: a quick fix after all? *Journal Of Applied Physiology (Bethesda, Md: 1985).* 2006;100(5):1439-1440. | Editorial |
| 16. | Boyce VL, Swinburn BA. The traditional Pima Indian diet. Composition and adaptation for use in a dietary intervention study. *Diabetes care.* 1993;16(1):369-371. | Did not address the main objective of the study |
| 17. | Bradley U, Spence M, Courtney CH, et al. Low-fat versus low-carbohydrate weight reduction diets: effects on weight loss, insulin resistance, and cardiovascular risk: a randomized control trial. *Diabetes.* 2009;58(12):2741-2748. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/771/CN-00733771/frame.html. | Study population without type 2 diabetes |
| 18. | Brehm BJ, Lattin BL, Summer SS, et al. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. *Diabetes care.* 2009;32(2):215-220. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/715/CN-00686715/frame.html. | Diet intervention not low-carbohydrate |
| 19. | Burani J, Longo PJ. Low-glycemic index carbohydrates: an effective behavioral change for glycemic control and weight management in patients with type 1 and 2 diabetes. *The Diabetes Educator.* 2006;32(1):78-88. | Not a randomized controlled trial; Did not address the main objective of the study |
| 20. | Cardot JM, Saffar F, Aiache JM. Influence of food on glycemia, insulin, C-peptide and glucagon levels in diabetic patients treated with antidiabetic metformin at steady-state. *Methods And Findings In Experimental And Clinical Pharmacology.* 1997;19(10):715-721. | Did not address the main objective of the study |
| 21. | Carty CL, Kooperberg C, Neuhouser ML, et al. Low-fat dietary pattern and change in body-composition traits in the Women's Health Initiative Dietary Modification Trial. *The American Journal Of Clinical Nutrition.* 2011;93(3):516-524. | Diet intervention not low-carbohydrate |
| 22. | Christensen AS, Viggers L, Hasselström K, Gregersen S. Effect of fruit restriction on glycemic control in patients with type 2 diabetes--a randomized trial. *Nutrition Journal.* 2013;12:29-29. | Diet intervention not low-carbohydrate |
| 23. | Chung HK, Chae JS, Hyun YJ, et al. Influence of adiponectin gene | Did not address the main objective of the study |

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| | polymorphisms on adiponectin level and insulin resistance index in response to dietary intervention in overweight-obese patients with impaired fasting glucose or newly diagnosed type 2 diabetes. *Diabetes care.* 2009;32(4):552-558. | |
| 24. | Clifton P. Effects of a high protein diet on body weight and comorbidities associated with obesity. *The British Journal Of Nutrition.* 2012;108 Suppl 2:S122-S129. | Did not address the main objective of the study; Not a randomized controlled trial |
| 25. | Coles LT, Fletcher EA, Galbraith CE, Clifton PM. Patient freedom to choose a weight loss diet in the treatment of overweight and obesity: a randomized dietary intervention in type 2 diabetes and pre-diabetes. *International Journal of Behavioral Nutrition and Physical Activity.* 2014;11(1):64. | Did not address the main objective of the study |
| 26. | Coppell KJ, Kataoka M, Williams SM, Chisholm AW, Vorgers SM, Mann JI. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment--Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. *BMJ (Clinical Research Ed).* 2010;341:c3337-c3337. | Diet intervention not low-carbohydrate |
| 27. | Craig LD, Nicholson S, SilVerstone FA, Kennedy RD. Use of a reduced-carbohydrate, modified-fat enteral formula for improving metabolic control and clinical outcomes in long-term care residents with type 2 diabetes: results of a pilot trial. *Nutrition (Burbank, Los Angeles County, Calif).* 1998;14(6):529-534. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/480/CN-00688480/frame.html. | Excluded due to enteral nutrition |
| 28. | Culling KS, Neil HAW, Gilbert M, Frayn KN. Effects of short-term low- and high-carbohydrate diets on postprandial metabolism in non-diabetic and diabetic subjects. *Nutrition, Metabolism, And Cardiovascular Diseases: NMCD.* 2009;19(5):345-351. | Duration less than 3 moths |
| 29. | Davies MJ, Metcalfe J, Day JL, Grenfell A, Hales CN, Gray IP. Improved beta cell function, with reduction in secretion of intact and 32/33 split proinsulin, after dietary intervention in subjects with type 2 diabetes mellitus. *Diabetic Medicine: A Journal Of The British Diabetic Association.* 1994;11(1):71-78. | Did not address the main objective of the study |

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| 30. | Davis JN, Ventura EE, Alexander KE, et al. Feasibility of a home-based versus classroom-based nutrition intervention to reduce obesity and type 2 diabetes in Latino youth. *International Journal Of Pediatric Obesity: IJPO: An Official Journal Of The International Association For The Study Of Obesity.* 2007;2(1):22-30. | Did not address the main objective of the study |
| 31. | Davis NJ, Cohen HW, Wylie-Rosett J, Stein D. Serum potassium changes with initiating low-carbohydrate compared to a low-fat weight loss diet in type 2 diabetes. *Southern Medical Journal.* 2008;101(1):46-49. | Duration less than 3 moths |
| 32. | Davis NJ, Crandall JP, Gajavelli S, et al. Differential effects of low-carbohydrate and low-fat diets on inflammation and endothelial function in diabetes. *Journal Of Diabetes And Its Complications.* 2011;25(6):371-376. | The study is included in the review with another publication |
| 33. | Davis NJ, Tomuta N, Isasi CR, Leung V, Wylie-Rosett J. Diabetes-specific quality of life after a low-carbohydrate and low-fat dietary intervention. *The Diabetes Educator.* 2012;38(2):250-255. | The study is included in the review with another publication |
| 34. | de Bont AJ, Baker IA, St Leger AS, et al. A randomised controlled trial of the effect of low fat diet advice on dietary response in insulin independent diabetic women. *Diabetologia.* 1981;21(6):529-533. | Published prior to 1983 |
| 35. | de Luis Román D, Izaola O, Aller R. [Assessment of the compliance of a 1,500 calorie diet in a population of overweight type-2 diabetics]. *Nutrición Hospitalaria.* 2001;16(4):122-125. | Not a randomized controlled trial |
| 36. | De Natale C, Annuzzi G, Bozzetto L, et al. Effects of a plant-based high-carbohydrate/high-fiber diet versus high-monounsaturated fat/low-carbohydrate diet on postprandial lipids in type 2 diabetic patients. *Diabetes Care.* 2009;32(12):2168-2173. | Did not address the main objective of the study |
| 37. | Dimitriadis E, Griffin M, Collins P, Johnson A, Owens D, Tomkin GH. Lipoprotein composition in NIDDM: effects of dietary oleic acid on the composition, oxidisability and function of low and high density lipoproteins. *Diabetologia.* 1996;39(6):667-676. | Did not address the main objective of the study |
| 38. | Dunstan DW, Mori TA, Puddey IB, et al. The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. *Diabetes Care.* 1997;20(6):913-921. | Multiple interventions (i.e. exercise) |

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| 39. | Dussol B, Iovanna C, Raccah D, et al. A randomized trial of low-protein diet in type 1 and in type 2 diabetes mellitus patients with incipient and overt nephropathy. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation.* 2005;15(4):398-406. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/220/CN-00561220/frame.html. | Did not address the main objective of the study |
| 40. | Dyson PA, Beatty S, Matthews DR. A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. *Diabetic Medicine: A Journal Of The British Diabetic Association.* 2007;24(12):1430-1435. | Study included individuals without type 2 diabetes |
| 41. | Eakin E, Reeves M, Winkler E, Lawler S, Owen N. Maintenance of physical activity and dietary change following a telephone-delivered intervention. *Health Psychology: Official Journal Of The Division Of Health Psychology, American Psychological Association.* 2010;29(6):566-573. | Did not address the main objective of the study |
| 42. | Educators AAoD. *Diabetes-specific Quality of Life After a Low-carbohydrate and Low-fat Dietary Intervention.* Sage CA: Los Angeles, CA: Sage Publications, Inc;2012. 0145-7217. | The study is included in the review with another publication |
| 43. | Escalante-Pulido M, Escalante-Herrera A, Milke-Najar ME, Alpizar-Salazar M. Effects of weight loss on insulin secretion and in vivo insulin sensitivity in obese diabetic and non-diabetic subjects. *Diabetes, Nutrition & Metabolism.* 2003;16(5-6):277-283. | Did not address the main objective of the study |
| 44. | Esposito K, Ciotola M, Maiorino MI, Giugliano D. Lifestyle approach for type 2 diabetes and metabolic syndrome. *Current Atherosclerosis Reports.* 2008;10(6):523-528. | Not a randomized controlled trial |
| 45. | Esposito K, Ida Maiorino M, Ciotola M, et al. Effects of a mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: A randomized trial. *Obstetrical and Gynecological Survey.* 2010;65(6):379-380. | Did not address the main objective of the study |
| 46. | Esposito K, Maiorino MI, Petrizzo M, Bellastella G, Giugliano D. The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. *Diabetes care.* 2014;37(7):1824-1830. | Did not address the main objective of the study |

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| 47. | Fabricatore AN, Wadden TA, Ebbeling CB, et al. Targeting dietary fat or glycemic load in the treatment of obesity and type 2 diabetes: a randomized controlled trial. *Diabetes Research And Clinical Practice.* 2011;92(1):37-45. | Diet intervention not low-carbohydrate |
| 48. | Faridi Z, Shuval K, Njike VY, et al. Partners reducing effects of diabetes (PREDICT): a diabetes prevention physical activity and dietary intervention through African-American churches. *Health Education Research.* 2010;25(2):306-315. | Did not address the main objective of the study |
| 49. | Feinman RD, Volek JS. Carbohydrate restriction as the default treatment for type 2 diabetes and metabolic syndrome. *Scandinavian Cardiovascular Journal: SCJ.* 2008;42(4):256-263. | Not a randomized controlled trial |
| 50. | Ferdowsian HR, Barnard ND, Hoover VJ, et al. A multicomponent intervention reduces body weight and cardiovascular risk at a GEICO corporate site. *American Journal Of Health Promotion: AJHP.* 2010;24(6):384-387. | Diet intervention not low-carbohydrate |
| 51. | Fitzgerald N, Damio G, Segura-Pérez S, Pérez-Escamilla R. Nutrition knowledge, food label use, and food intake patterns among Latinas with and without type 2 diabetes. *Journal Of The American Dietetic Association.* 2008;108(6):960-967. | Did not address the main objective of the study |
| 52. | Fransen MP, von Wagner C, Essink-Bot M-L. Diabetes self-management in patients with low health literacy: ordering findings from literature in a health literacy framework. *Patient Education And Counseling.* 2012;88(1):44-53. | Did not address the main objective of the study |
| 53. | Franz MJ, Monk A, Barry B, et al. Effectiveness of Medical Nutrition Therapy Provided by Dietitians in the Management of Non–Insulin-Dependent Diabetes Mellitus: A Randomized, Controlled Clinical Trial. *Journal of the American Dietetic Association.* 1995;95(9):1009-1017. | Information on dietary composition is not provided |
| 54. | Fraser A, Abel R, Lawlor DA, Fraser D, Elhayany A. A modified Mediterranean diet is associated with the greatest reduction in alanine aminotransferase levels in obese type 2 diabetes patients: Results of a quasi-randomised controlled trial. *Diabetologia.* 2008;51(9):1616-1622. | The study is included in the review with another publication |
| 55. | Gaede P, Beck M, Vedel P, Pedersen O. Limited impact of lifestyle education in patients with Type 2 diabetes mellitus and | Diet intervention not low-carbohydrate |

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| | microalbuminuria: results from a randomized intervention study. *Diabetic Medicine: A Journal Of The British Diabetic Association.* 2001;18(2):104-108. | |
| 56. | Gaetke LM, Stuart MA, Truszczynska H. A single nutrition counseling session with a registered dietitian improves short-term clinical outcomes for rural Kentucky patients with chronic diseases. *Journal Of The American Dietetic Association.* 2006;106(1):109-112. | Did not address the main objective of the study |
| 57. | Gallagher A, Henderson W, Abraira C. Dietary patterns and metabolic control in diabetic diets: a prospective study. *Journal Of The American College Of Nutrition.* 1987;6(6):525-532. | Did not address the main objective of the study |
| 58. | Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. *Diabetes.* 2004;53(9):2375-2382. | Duration less than 3 moths |
| 59. | Garg A, Grundy SM, Unger RH. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. *Diabetes.* 1992;41(10):1278-1285. | Duration less than 3 moths |
| 60. | Gerhard GT, Ahmann A, Meeuws K, McMurry MP, Duell PB, Connor WE. Effects of a low-fat diet compared with those of a high-monounsaturated fat diet on body weight, plasma lipids and lipoproteins, and glycemic control in type 2 diabetes. *The American Journal Of Clinical Nutrition.* 2004;80(3):668-673. | Duration less than 3 moths |
| 61. | Gibb AL, Welfare W. Low carbohydrate diets and diabetes control. *The British Journal Of General Practice: The Journal Of The Royal College Of General Practitioners.* 2006;56(522):57-58. | Not a randomized controlled trial |
| 62. | Gillen LJ, Tapsell LC, Patch CS, Owen A, Batterham M. Structured dietary advice incorporating walnuts achieves optimal fat and energy balance in patients with type 2 diabetes mellitus. *Journal Of The American Dietetic Association.* 2005;105(7):1087-1096. | Diet intervention not low-carbohydrate |
| 63. | Golan R, Tirosh A, Schwarzfuchs D, et al. Dietary intervention induces flow of changes within biomarkers of lipids, inflammation, liver enzymes, and glycemic control. *Nutrition (Burbank, Los Angeles County, Calif).* 2012;28(2):131-137. | The study is included in the review with another publication |
| 64. | Goode AD, Winkler EAH, Lawler SP, Reeves MM, Owen N, Eakin EG. A | Did not address the main objective of the study |

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|---|---|---|
| | telephone-delivered physical activity and dietary intervention for type 2 diabetes and hypertension: does intervention dose influence outcomes? *American Journal Of Health Promotion: AJHP.* 2011;25(4):257-263. | |
| 65. | Gougeon R, Carrington M, Field CJ. The impact of low-carbohydrate diets on glycemic control and weight management in patients with type 2 diabetes. *Canadian Journal of Diabetes.* 2006;30(3):269-277. | Not a randomized controlled trial |
| 66. | Guldbrand H, Lindström T, Dizdar B, et al. Randomization to a low-carbohydrate diet advice improves health related quality of life compared with a low-fat diet at similar weight-loss in Type 2 diabetes mellitus. *Diabetes research and clinical practice.* 2014;106(2):221-227. | The study is included in the review with another publication |
| 67. | Günther ALB, Liese AD, Bell RA, et al. Association between the dietary approaches to hypertension diet and hypertension in youth with diabetes mellitus. *Hypertension.* 2009;53(1):6-12. | Did not address the main objective of the study |
| 68. | Gustafson C. Curing TYPE 2 DIABETES WITH FOOD. *Natural Solutions.* 2011(139):44-48. | Not a randomized controlled trial |
| 69. | Gutierrez M, Akhavan M, Jovanovic L, Peterson CM. Utility of a short-term 25% carbohydrate diet on improving glycemic control in type 2 diabetes mellitus. *Journal Of The American College Of Nutrition.* 1998;17(6):595-600. | Duration less than 3 moths |
| 70. | Haimoto H, Iwata M, Wakai K, Umegaki H. Long-term effects of a diet loosely restricting carbohydrates on HbA1c levels, BMI and tapering of sulfonylureas in type 2 diabetes: a 2-year follow-up study. *Diabetes Research And Clinical Practice.* 2008;79(2):350-356. | Diet intervention not low-carbohydrate |
| 71. | Haimoto H, Sasakabe T, Wakai K, Umegaki H. Effects of a low-carbohydrate diet on glycemic control in outpatients with severe type 2 diabetes. *Nutrition & Metabolism.* 2009;6:1-5. | Not a randomized controlled trial |
| 72. | He YN, Feskens E, Li YP, et al. Association between high fat-low carbohydrate diet score and newly diagnosed type 2 diabetes in Chinese population. *Biomedical And Environmental Sciences: BES.* 2012;25(4):373-382. | Not a randomized controlled trial |
| 73. | Heilbronn LK, Noakes M, Clifton PM. Effect of energy restriction, weight loss, and diet composition on plasma lipids and glucose in patients with type 2 diabetes. *Diabetes care.* 1999;22(6):889-895. | Diet intervention not low-carbohydrate |

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| | http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/386/CN-00164386/frame.html. | |
| 74. | Helge JW, Tobin L, Drachmann T, Hellgren LI, Dela F, Galbo H. Muscle ceramide content is similar after 3 weeks' consumption of fat or carbohydrate diet in a crossover design in patients with type 2 diabetes. *European Journal Of Applied Physiology.* 2012;112(3):911-918. | Duration less than 3 moths |
| 75. | Higashi K, Shige H, Ito T, et al. Effect of a low-fat diet enriched with oleic acid on postprandial lipemia in patients with type 2 diabetes mellitus. *Lipids.* 2001;36(1):1-6. | Did not address the main objective of the study |
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| 79. | Hsieh CJ, Wang PW. Effectiveness of weight loss in the elderly with type 2 diabetes mellitus. *Journal Of Endocrinological Investigation.* 2005;28(11):973-977. | Multiple interventions (i.e. exercise) |
| 80. | Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition (Burbank, Los Angeles County, Calif).* 2012;28(10):1016-1021. | Not a randomized controlled trial |
| 81. | Imai S, Matsuda M, Hasegawa G, et al. A simple meal plan of 'eating vegetables before carbohydrate' was more effective for achieving glycemic control than an exchange-based meal plan in Japanese patients with type 2 diabetes. *Asia Pacific journal of clinical nutrition.* 2011;20(2):161-168. | Did not address the main objective of the study |

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| | http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/342/CN-00799342/frame.html. | |
| 82. | Iqbal N, Vetter ML, Moore RH, et al. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. *Obesity (Silver Spring, Md).* 2010;18(9):1733-1738. | The control-diet contains 40% of energy from carbohydrates |
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| 96. | Lim JH, Lee Y-S, Chang HC, Moon MK, Song Y. Association between dietary patterns and blood lipid profiles in Korean adults with type 2 diabetes. *Journal Of Korean Medical Science.* 2011;26(9):1201-1208. | Not a randomized controlled trial; Did not address the main objective of the study |
| 97. | Lousley SE, Jones DB, Slaughter P. High carbohydrate-high fibre diets in poorly controlled diabetes. *Diabetic Medicine.* 1984;1(1):21-25. | Duration less than 3 moths |
| 98. | Luscombe ND, Parker B, Clifton PM, Noakes M, Wittert G. Effects of Energy-Restricted Diets Containing Increased Protein on Weight Loss, Resting Energy Expenditure, and the Thermic Effect of Feeding in Type 2 Diabetes. *Diabetes Care.* 2002;25(4):652. | Diet intervention not low-carbohydrate |
| 99. | Ma Y, Olendzki BC, Chiriboga D, et al. PDA-assisted low glycemic index dietary intervention for type II diabetes: a pilot study. *European Journal Of Clinical Nutrition.* 2006;60(10):1235-1243. | Did not address the main objective of the study |

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| 100. | Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, Chisholm DJ. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. *Diabetes Care.* 1998;21(5):687-694. | Duration less than 3 moths |
| 101. | McAuley KA, Hopkins CM, Smith KJ, et al. Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. *Diabetologia.* 2005;48(1):8-16. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/033/CN-00514033/frame.html. | Study population without type 2 diabetes |
| 102. | McCarron DA. Nutritional management of cardiovascular risk factors. A randomized clinical trial. *Archives of internal medicine.* 1997;157(2):169-177. | Diet intervention not low-carbohydrate |
| 103. | McVay MA, Voils CI, Coffman CJ, et al. Factors associated with choice of a low-fat or low-carbohydrate diet during a behavioral weight loss intervention. *Appetite.* 2014;83:117-124. | Did not address the main objective of the study |
| 104. | Merino J, Kones R, Ferré R, et al. Negative effect of a low-carbohydrate, high-protein, high-fat diet on small peripheral artery reactivity in patients with increased cardiovascular risk. *British Journal of Nutrition.* 2013;109(7):1241-1247. | Not a randomized controlled trial; Did not address the main objective of the study |
| 105. | Milne RM, Mann JI, Chisholm AW, Williams SM. Long-Term Comparison of Three Dietary Prescriptions in the Treatment of NIDDM. *Diabetes Care.* 1994;17(1):74-80. | Diet intervention not low-carbohydrate |
| 106. | Moreno B, Bellido D, Sajoux I, et al. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine.* 2014;47(3):793-805. | Study population without type 2 diabetes |
| 107. | Mori TA, Dunstan DW, Burke V, et al. Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin-dependent diabetic patients. *Metabolism: Clinical And Experimental.* 1999;48(11):1402-1408. | Did not address the main objective of the study |
| 108. | Mraz M, Lacinova Z, Drapalova J, et al. The effect of very-low-calorie diet on mRNA expression of inflammation-related genes in subcutaneous adipose tissue and peripheral monocytes of obese patients with type 2 diabetes mellitus. *The Journal Of Clinical Endocrinology And Metabolism.* 2011;96(4):E606-E613. | Did not address the main objective of the study |

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| 109. | Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S. Toward improved management of NIDDM: A randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Preventive Medicine.* 1999;29(2):87-91. | Diet intervention not low-carbohydrate |
| 110. | Nielsen JV, Joensson E. Low-carbohydrate diet in type 2 diabetes. Stable improvement of bodyweight and glycemic control during 22 months follow-up. *Nutrition & Metabolism.* 2006;3:22-25. | Not a randomized controlled trial |
| 111. | Nielsen JV, Jönsson E, Nilsson A-K. Lasting improvement of hyperglycaemia and bodyweight: low-carbohydrate diet in type 2 diabetes. A brief report. *Upsala Journal Of Medical Sciences.* 2005;110(2):179-183. | Not a randomized controlled trial |
| 112. | Nnadi IM, Fasanmade AA, Adeleye J, Nnoka KO, Keshinro OO. Low Carbohydrate Diet Lowers Blood Glucose in Type II Diabetes Mellitus Subjects. *Journal of the Academy of Nutrition & Dietetics.* 2012;112:A34-A34. | Diet intervention not low-carbohydrate |
| 113. | Nuttall FQ. The high-carbohydrate diet in diabetes management. *Advances In Internal Medicine.* 1988;33:165-183. | Not a randomized controlled trial |
| 114. | Nuttall FQ, Gannon MC. Effect of a LoBAG30 diet on protein metabolism in men with type 2 diabetes. A Randomized Controlled Trial. *Nutrition and Metabolism.* 2012;9(43). | Duration less than 3 moths |
| 115. | Oberg EB, Bradley RD, Allen J, McCrory MA. CAM: naturopathic dietary interventions for patients with type 2 diabetes. *Complementary Therapies In Clinical Practice.* 2011;17(3):157-161. | Not a randomized controlled trial |
| 116. | O'Brien T, Nguyen TT, Buithieu J, Kottke BA. Lipoprotein compositional changes in the fasting and postprandial state on a high-carbohydrate low-fat and a high-fat diet in subjects with noninsulin-dependent diabetes mellitus. *The Journal Of Clinical Endocrinology And Metabolism.* 1993;77(5):1345-1351. | Duration less than 3 moths |
| 117. | O'Dea K, Traianedes K, Ireland P, et al. The effects of diet differing in fat, carbohydrate, and fiber on carbohydrate and lipid metabolism in type II diabetes. *Journal Of The American Dietetic Association.* 1989;89(8):1076-1086. | Duration less than 3 moths |
| 118. | Oldroyd JC, Unwin NC, White M, Mathers JC, Alberti KGMM. Randomised | Diet intervention not low-carbohydrate |

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| | controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. *Diabetes Research And Clinical Practice.* 2006;72(2):117-127. | |
| 119. | Pacy PJ, Dodson PM, Fletcher RF. Effect of a high carbohydrate, low sodium and low fat diet in type 2 diabetics with moderate hypertension. *International Journal Of Obesity.* 1986;10(1):43-52. | Diet intervention not low-carbohydrate |
| 120. | Pacy PJ, Dodson PM, Kubicki AJ, Fletcher RF, Taylor KG. Comparison of the hypotensive and metabolic effects of metoprolol therapy with a high fibre, low sodium, low fat diet in hypertensive type 2 diabetic subjects. *Diabetes Research (Edinburgh, Scotland).* 1984;1(4):201-207. | Did not address the main objective of the study |
| 121. | Pacy PJ, Dodson PM, Kubicki AJ, Fletcher RF, Taylor KG. High fibre, low sodium and low fat diet in white and black type 2 diabetics with mild hypertension. *Diabetes Research (Edinburgh, Scotland).* 1986;3(6):287-292. | Did not address the main objective of the study |
| 122. | Papakonstantinou E, Triantafillidou D, Panagiotakos DB, et al. A high-protein low-fat diet is more effective in improving blood pressure and triglycerides in calorie-restricted obese individuals with newly diagnosed type 2 diabetes. *European Journal of Clinical Nutrition.* 2010;64(6):595-602. | Did not address the main objective of the study |
| 123. | Parker B, Noakes M, Luscombe N, Clifton P. Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. *Diabetes Care.* 2002;25(3):425-430. | The study is included in the review with another publication |
| 124. | Pawlak R. Low-carbohydrate, high-protein diets for management of type 2 diabetes. *The American journal of clinical nutrition.* 2013;98(1):247-248. | Not a randomized controlled trial |
| 125. | Petersen KF DS. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. 2005. | Did not address the main objective of the study |
| 126. | Peterson DB, Lambert J, Gerring S, et al. Sucrose in the diet of diabetic patients--just another carbohydrate? *Diabetologia.* 1986;29(4):216-220. | Did not address the main objective of the study |
| 127. | Pfeiffer A. High-fat diets in diabetes. *Deutsche medizinische Wochenschrift (1946).* 2013;138(18):964-966. | Not a randomized controlled trial |
| 128. | Pohl M, Mayr P, Mertl-Roetzer M, et al. Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of | Excluded due to enteral nutrition |

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| | a randomized, controlled multicenter trial. *JPEN Journal Of Parenteral And Enteral Nutrition.* 2009;33(1):37-49. | |
| 129. | Pohl M, Mayr P, Mertl-Roetzer M, et al. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. *European Journal of Clinical Nutrition.* 2005;59(11):1221-1232. | Excluded due to enteral nutrition |
| 130. | Quandt SA, Bell RA, Snively BM, Vitolins MZ, Wetmore-Arkader LK, Arcury TA. Dietary fat reduction behaviors among African American, American Indian, and white older adults with diabetes. *Journal Of Nutrition For The Elderly.* 2009;28(2):143-157. | Not a randomized controlled trial |
| 131. | Radulian G, Rusu E, Dragomir AD, Stoian M, Vladica M. The Effects of Low Carbohydrate Diet as Compared with a Low Fat Diet in Elderly Patients with Type 2 Diabetes Mellitus. *Diabetes.* 2007;56:A448-A448. | Poster |
| 132. | Ramadas A, Quek KF, Chan CKY, Oldenburg B, Hussein Z. Randomised-controlled trial of a web-based dietary intervention for patients with type 2 diabetes mellitus: study protocol of myDIDeA. *BMC Public Health.* 2011;11:359-359. | Diet intervention not low-carbohydrate |
| 133. | Rivellese AA, Giacco R, Genovese S, et al. Effects of changing amount of carbohydrate in diet on plasma lipoproteins and apolipoproteins in type II diabetic patients. *Diabetes Care.* 1990;13(4):446-448. | Duration less than 3 moths |
| 134. | Rodríguez-Villar C, Manzanares JM, Casals E, et al. High-monounsaturated fat, olive oil-rich diet has effects similar to a high-carbohydrate diet on fasting and postprandial state and metabolic profiles of patients with type 2 diabetes. *Metabolism: Clinical And Experimental.* 2000;49(12):1511-1517. | Duration less than 3 moths |
| 135. | Root MM, Dawson HR. DASH-like diets high in protein or monounsaturated fats improve metabolic syndrome and calculated vascular risk. *Int J Vitam Nutr Res.* 2013;83(4):224-231. | Did not address the main objective of the study |
| 136. | Ruth MR, Port AM, Shah M, et al. Consuming a hypocaloric high fat low carbohydrate diet for 12 weeks lowers C-reactive protein, and raises serum adiponectin and high density lipoprotein-cholesterol in obese subjects. *Metabolism-Clinical and Experimental.* 2013;62(12):1779-1787. | Study population without type 2 diabetes |

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| 137. | Salas-Salvadó J, Bulló M, Babio N, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care.* 2011;34(1):14-19. | Diet intervention not low-carbohydrate |
| 138. | Sanders TAB. High- versus low-fat diets in human diseases. *Current Opinion In Clinical Nutrition And Metabolic Care.* 2003;6(2):151-155. | Not a randomized controlled trial |
| 139. | Sanz-París A, Calvo L, Guallard A, Salazar I, Albero R. High-fat versus high-carbohydrate enteral formulae: effect on blood glucose, C-peptide, and ketones in patients with type 2 diabetes treated with insulin or sulfonylurea. *Nutrition (Burbank, Los Angeles County, Calif).* 1998;14(11-12):840-845. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/433/CN-00157433/frame.html. | Duration less than 3 moths |
| 140. | Saslow LR, Kim S, Daubenmier JJ, et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. *PloS one.* 2014;9(4):e91027. | Study population with pre-diabetes and diabetes (separate data for participants with type 2 diabetes was not provided) |
| 141. | Saslow LR, Kim S, Daubenmier JJ, et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. *PloS one.* 2014;9(4):e91027. | Duplicate |
| 142. | Schrauwen P, Schaart G, Saris WH, et al. The effect of weight reduction on skeletal muscle UCP2 and UCP3 mRNA expression and UCP3 protein content in Type II diabetic subjects. *Diabetologia.* 2000;43(11):1408-1416. | Did not address the main objective of the study |
| 143. | Sears B, Kahl P, Rapier G. The San Antonio Type 2 Diabetic Study. *International Journal of Applied Kinesiology & Kinesiologic Medicine.* 2006(21):66-67. | Not a randomized controlled trial |
| 144. | Shahar DR, Abel R, Elhayany A, Vardi H, Fraser D. Does dairy calcium intake enhance weight loss among overweight diabetic patients? *Diabetes Care.* 2007;30(3):485-489. | The study is included in the review with another publication |
| 145. | Sharafetdinov KK, Plotnikova OA, Kulakova SN, Alekseeva RI, Meshcheriakova VA, Mal'tsev GI. [Effect of a monounsaturated fatty acids-enriched diet on the clinical and metabolic parameters in type 2 diabetic patients]. *Voprosy Pitaniia.* 2003;72(4):20-24. | Not a randomized controlled trial; Diet intervention not low-carbohydrate |

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| 146. | Shige H, Nestel P, Sviridov D, Noakes M, Clifton P. Effect of weight reduction on the distribution of apolipoprotein A-I in high-density lipoprotein subfractions in obese non-insulin-dependent diabetic subjects. *Metabolism: Clinical And Experimental.* 2000;49(11):1453-1459. | Diet intervention not low-carbohydrate |
| 147. | Spritzler F. A Low-Carbohydrate, Whole-Foods Approach to Managing Diabetes and Prediabetes. *Diabetes Spectrum.* 2012;25(4):238-243. | Not a randomized controlled trial |
| 148. | Stacpoole PW. Should NIDDM patients be on high-carbohydrate, low-fat diets? Affirmative. *Hospital Practice (Office Ed).* 1992;27 Suppl 1:6-10. | Did not address the main objective of the study |
| 149. | Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care.* 2001;24(4):619-624. | Did not address the main objective of the study |
| 150. | Tapsell LC, Gillen LJ, Patch CS, et al. Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes. *Diabetes Care.* 2004;27(12):2777-2783. | Diet intervention not low-carbohydrate |
| 151. | Tirosh A, Golan R, Harman-Boehm I, et al. Renal function following three distinct weight loss dietary strategies during 2 years of a randomized controlled trial. *Diabetes care.* 2013;36(8):2225-2232. | The study is included in the review with another publication |
| 152. | Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA: The Journal Of The American Medical Association.* 1999;281(21):2005-2012. | Diet intervention not low-carbohydrate; Did not address the main objective of the study |
| 153. | Vadstrup ES, Frølich A, Perrild H, Borg E, Røder M. Lifestyle intervention for type 2 diabetes patients: trial protocol of The Copenhagen Type 2 Diabetes Rehabilitation Project. *BMC Public Health.* 2009;9:166-166. | Multiple interventions implemented |
| 154. | Vestli-Nielsen J. Ett logiskt val vid typ 2 diabetes - protein och fett i stället för kolhydrat?. . *Tidskr Medikam.* 2004;9:9-10. | Did not address the main objective of the study |
| 155. | Viviani GL, Carta G, Berri F, et al. Effects of normoglycemia after a low carbohydrate diet in NIDDM. Insulin secretion and effectiveness. *Minerva Endocrinologica.* 1984;9(2):229-232. | Did not address the main objective of the study |
| 156. | Vlachos D, Ganotopoulou A, Stathi C, et al. A low-carbohydrate protein sparing modified fast diet compared with a low glycaemic index reduced calorie diet in obese type 2 diabetic patients. *Diabetologia.* 2011;54:S355. | Conference abstract |

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| 157. | Vuksan V, Jenkins DJ, Spadafora P, et al. Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial. *Diabetes Care.* 1999;22(6):913-919. | Did not address the main objective of the study |
| 158. | Wolever T, Gibbs A, Chiasson J-L, et al. Altering source or amount of dietary carbohydrate has acute and chronic effects on postprandial glucose and triglycerides in type 2 diabetes: Canadian trial of Carbohydrates in Diabetes (CCD). *Nutrition, Metabolism and Cardiovascular Diseases.* 2013;23(3):227-234. | The study is included in the review with another publication |
| 159. | Wolever T, Mehling C, Chiasson JL, et al. Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of Carbohydrates in Diabetes): a randomised controlled trial. *Diabetologia.* 2008;51(9):1607-1615. | The study is included in the review with another publication |
| 160. | Wolever TM, Chiasson JL, Josse RG, et al. No relationship between carbohydrate intake and effect of acarbose on HbA1c or gastrointestinal symptoms in type 2 diabetic subjects consuming 30-60% of energy from carbohydrate. *Diabetes care.* 1998;21(10):1612-1618. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/642/CN-00155642/frame.html. | Diet intervention not low-carbohydrate |
| 161. | Wycherley TP, Noakes M, Clifton PM, Cleanthous X, Keogh JB, Brinkworth GD. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. *Diabetes Care.* 2010;33(5):969-976. | Multiple interventions (i.e. exercise) |
| 162. | Yancy Jr WS, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutrition & Metabolism.* 2005;2:34-37. | Not a randomized controlled trial |
| 163. | Yancy Jr WS, Westman EC, McDuffie JR, et al. A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. *Archives of internal medicine.* 2010;170(2):136-145. | Multiple interventions (i.e. orlistat) |
| 164. | Ziemer DC, Berkowitz KJ, Panayioto RM, et al. A simple meal plan emphasizing healthy food choices is as effective as an exchange-based meal plan for urban African Americans with type 2 diabetes. *Diabetes Care.* 2003;26(6):1719-1724. | Diet intervention not low-carbohydrate |

**Supplementary table 3A** Subgroup-analysis based on study duration ≤6 months (short term) vs ≥12 moths (long term)

| Outcome | Short term | Long term | Test for subgroup effect | |
|---|---|---|---|---|
| | MD (95 % CI) | MD (95 % CI) | p-value | $I^2$ |
| Weight [kg] | -0.87 [-1.88, 0.15] | 0.14 [-0.29, 0.57] | 0.07* | 69.0% |
| BMI [kg/m2] | -1.21 [-2.73, 0.32] | -0.69 [-1.51, 0.13] | 0.56 | 0% |
| HbA1c [%] | -0.17 [-0.27, -0.08] | -0.00 [-0.10, 0.09] | 0.01* | 83.7% |
| LDL [mmol/l] | -0.08 [-0.29, 0.14] | 0.03 [-0.10, 0.16] | 0.40 | 0% |
| HDL [mmol/l] | -0.01 [-0.07, 0.04] | 0.06 [-0.01, 0.13] | 0.10* | 64.1% |
| Total cholesterol [mmol/l] | -0.06 [-0.41, 0.30] | 0.07 [-0.04, 0.19] | 0.49 | 0% |
| Triacylglycerol [mmol/l] | -0.18 [-0.36, 0.00] | -0.10 [-0.23, 0.03] | 0.48 | 0% |
| SBP [mmHg] | -0.33 [-2.31, 1.65] | -1.39 [-3.20, 0.43] | 0.44 | 0% |
| DBP [mmHg] | -0.06 [-1.46, 1.34] | -0.55 [-2.17, 1.06] | 0.65 | 0% |

**Supplementary table 3B:** Subgroup-analysis based on the amount of carbohydrates in the LCD group, LCD (21-70 g CHO) vs LCD (30-40% TE CHO)

| Outcome | Moderate LCD | VLCD | Test for subgroup effect | |
|---|---|---|---|---|
| | MD (95 % CI) | MD (95 % CI) | p-value | $I^2$ |
| Weight [kg] | -0.10 (-0.46, 0.26) | -0.66 (-1.99, 0.68) | 0.43 | 0% |
| BMI [kg/m2] | -0.68 (-1.81, 0.44) | -1.82 (-3.51, -0.13) | 0.27 | 16.9% |
| HbA1c [%] | -0.07 (-0.17, 0.04) | -0.23 (-0.48, 0.02) | 0.23 | 31.6% |
| LDL [mmol/l] | -0.06 (-0.19, 0.07) | 0.16 (-0.02, 0.34) | 0.05* | 73.8% |
| HDL [mmol/l] | 0.03 (-0.03, 0.10) | 0.07 (0.00, 0.13) | 0.46 | 0% |
| Total cholesterol [mmol/l] | -0.01 (-0.20, 0.17) | 0.17 (-0.02, 0.37) | 0.17 | 45.7% |
| Triacylglycerol [mmol/l] | -0.10 (-0.23, 0.03) | -0.23 (-0.45, -0.02) | 0.29 | 10.1% |
| SBP [mmHg] | -0.92 (-2.32, 0.47) | -0.99 (-4.77, 2.79) | 0.98 | 0% |
| DBP [mmHg] | -0.06 (-1.13, 1.01) | -1.19 (-3.90, 1.52) | 0.44 | 0% |

**Supplemantary table 3C:** Sensitivity analyses high versus low risk of bias

| Outcome | Low RoB | High RoB | P-value | I^2 |
|---|---|---|---|---|
| Weight | 0.86 [-1.86, 3.57] | -1.75 [-2.82, -0.69] | 0,08 | 67,5 |
| HbA1c | 0.12 [-0.12, 0.35] | -0.30 [-0.54, -0.07] | 0,01 | 83,6 |
| LDL | 0.10 [-0.11, 0.31] | -0.05 [-0.25, 0.16] | 0,34 | 0 |
| HDL | 0.04 [-0.02, 0.09] | -0.12 [-0.23, -0.01] | 0,01 | 83,2 |
| TC | 0.10 [-0.14, 0.33] | 0.07 [-0.13, 0.27] | 0,86 | 0 |
| Triglyc | 0.06 [0.00, 0.12] | -0.26 [-0.41, -0.12] | <0,0001 | 93,8 |
| SBP | -2.57 [-7.21, 2.07] | -2.69 [-6.93, 1.55] | 0,97 | 0 |
| DBP | -0.48 [-2.51, 1.55] | -2.38 [-6.04, 1.28] | 0,37 | 0 |
| Compliance | 1.08 [0.83, 1.42] | 1.03 [0.80, 1.33] | 0,79 | 0 |

**Carbohydrate quantity in the dietary management of type 2 diabetes**

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Anticipated absolute effects | |
|---|---|---|---|---|
| | | | Risk with HCD | Risk difference with LCD |
| Weight<br>follow up: 3 months to 3 ± 1.8 years | 1587<br>(17 RCTs) | ⨁⨁⨁◯<br>MODERATE [a] | The mean weight was **86.4** kg | MD **0.35 kg lower**<br>(0.91 lower to 0.21 higher) |
| HbA1c<br>follow up: 3 months to 24 months | 1425<br>(16 RCTs) | ⨁⨁⨁◯<br>MODERATE [a] | The mean HbA1c was **7.2** % | MD **0.09 % lower**<br>(0.17 lower to 0.01 lower) |
| LDL-cholesterol<br>follow up: 3 months to 3 ± 1.8 years | 1409<br>(15 RCTs) | ⨁⨁◯◯<br>LOW [a,b] | The mean LDL-cholesterol was **2.68** mmol/l | MD **0.01 mmol/l lower**<br>(0.13 lower to 0.11 higher) |
| HDL-cholesterol<br>follow up: 3 months to 3 ± 1.8 years | 1438<br>(16 RCTs) | ⨁⨁◯◯<br>LOW [a,c] | The mean HDL-cholesterol was **1.17** mmol/l | MD **0.04 mmol/l higher**<br>(0.01 lower to 0.1 higher) |

| Outcomes | № of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Anticipated absolute effects | |
|---|---|---|---|---|
| | | | Risk with HCD | Risk difference with LCD |
| Total cholesterol<br>follow up: 3 months to 3 ± 1.8 years | 1373<br>(14 RCTs) | ⊕⊕◯◯<br>LOW [a,d] | The mean total cholesterol was **4.62** mmol/l | MD **0.04 mmol/l higher**<br>(0.12 lower to 0.2 higher) |
| Triacylglycerol<br>follow up: 3 months to 24 months | 1391<br>(16 RCTs) | ⊕⊕◯◯<br>LOW [a,e] | The mean triacylglycerol was **1.59** mmol/l | MD **0.13 mmol/l lower**<br>(0.24 lower to 0.02 lower) |
| Systolic blood pressure<br>follow up: 3 months to 24 months | 1179<br>(14 RCTs) | ⊕⊕⊕◯<br>MODERATE [a] | The mean systolic blood pressure was **129.7** mmHg | MD **0.93 mmHg lower**<br>(2.24 lower to 0.37 higher) |
| Diastolic blood pressure<br>follow up: 3 months to 24 months | 944<br>(12 RCTs) | ⊕⊕⊕◯<br>MODERATE [a] | The mean diastolic blood pressure was **75.4** mmHg | MD **0.21 mmHg lower**<br>(1.2 lower to 0.79 higher) |

## Explanations

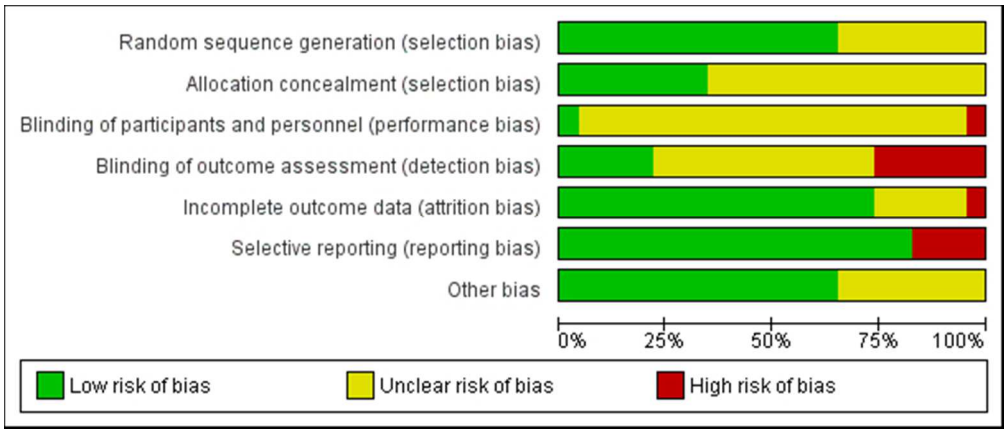
a. Downgraded by one level due to risk of bias: The majority of evidence is from studies at high- or unclear risk of bias

b. Downgraded by one level due to inconsistency: Substantial heterogeneity (I2 statistics 64%, $p < 0.001$) and limited overlap of CI

c. Downgraded by one level due to inconsistency: Substantial heterogeneity (I2 statistics 72%, p < 0.001) and limited overlap of CI

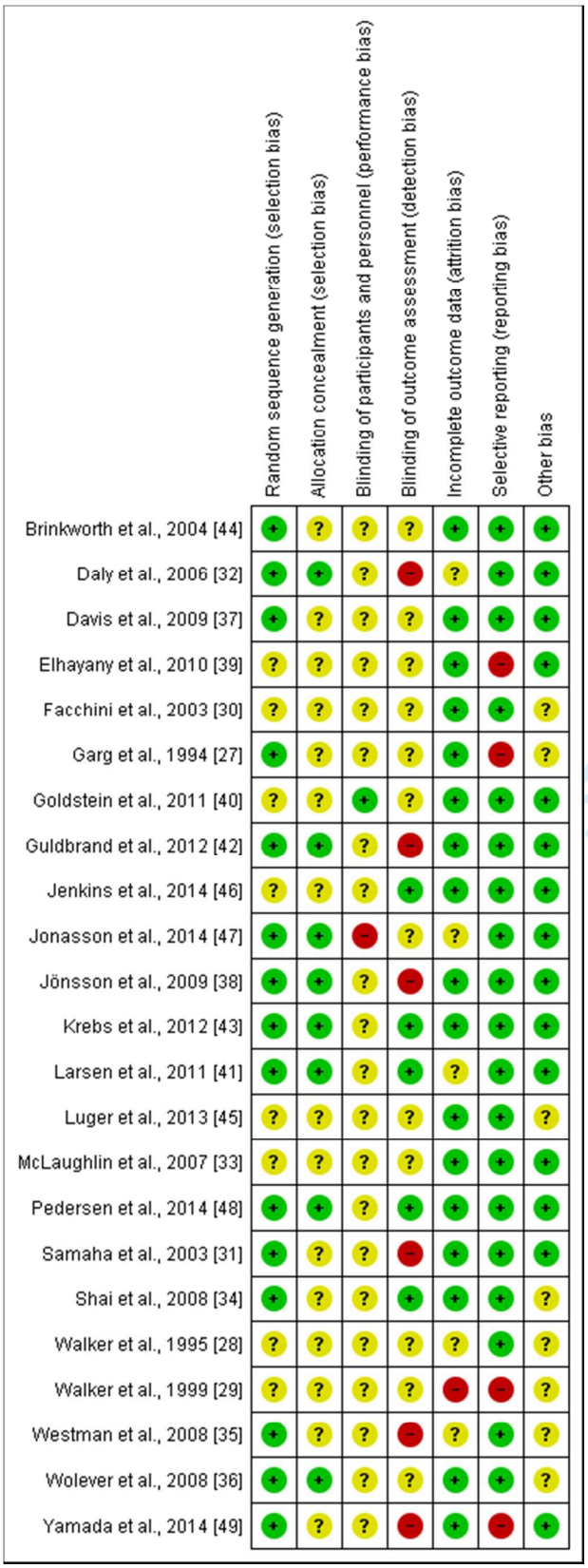
d. Downgraded by one level due to inconsistency: Substantial heterogeneity (I2 statistics 71%, p < 0.001) and limited overlap of CI

e. Downgraded by one level due to inconsistency: Substantial heterogeneity (I2 statistics 57%, p = 0.003) and limited overlap of CI

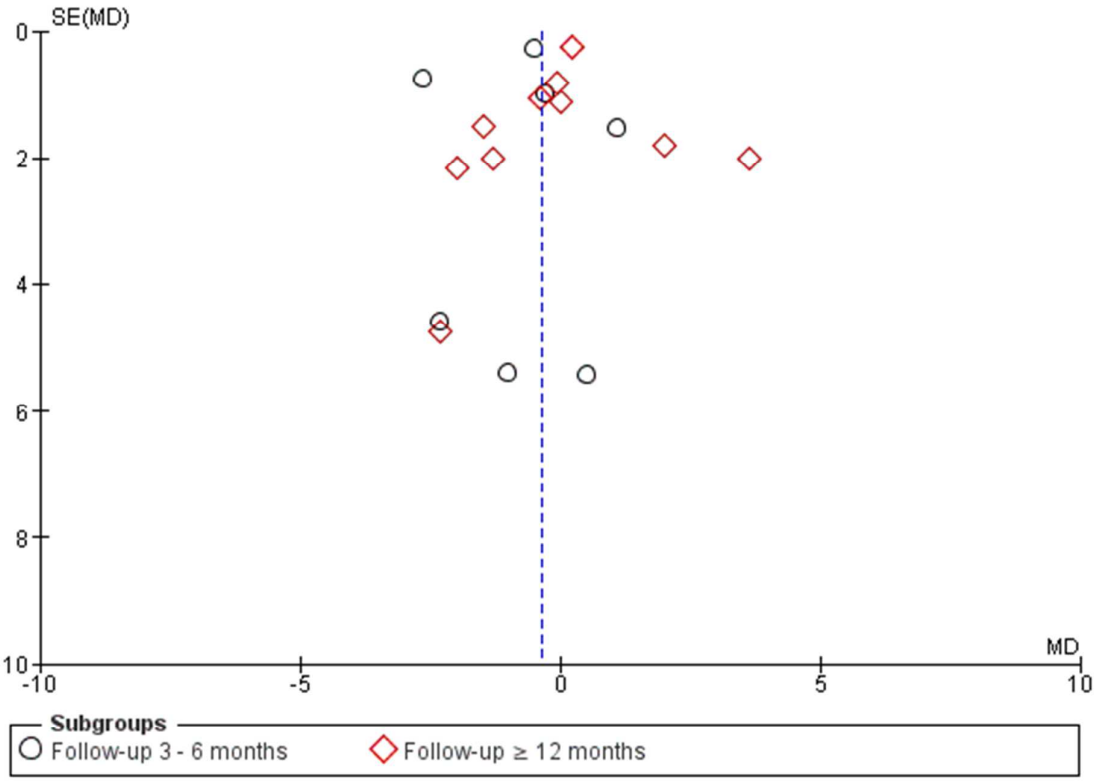



213x90mm (72 x 72 DPI)

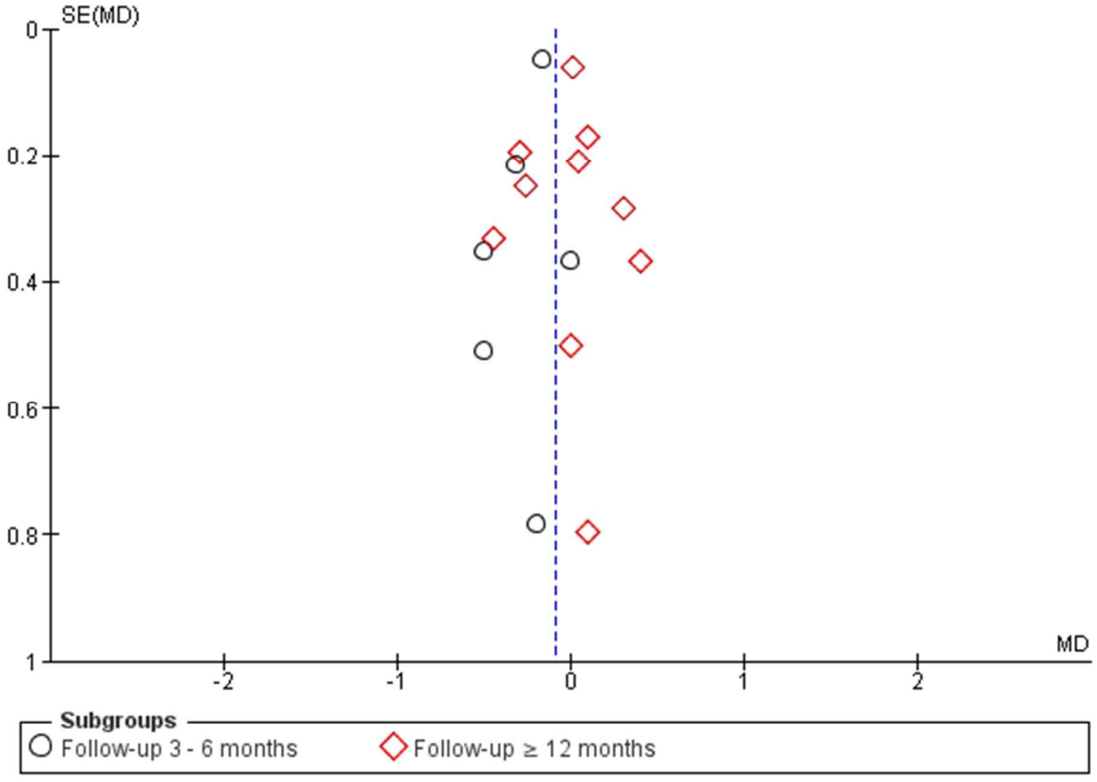
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



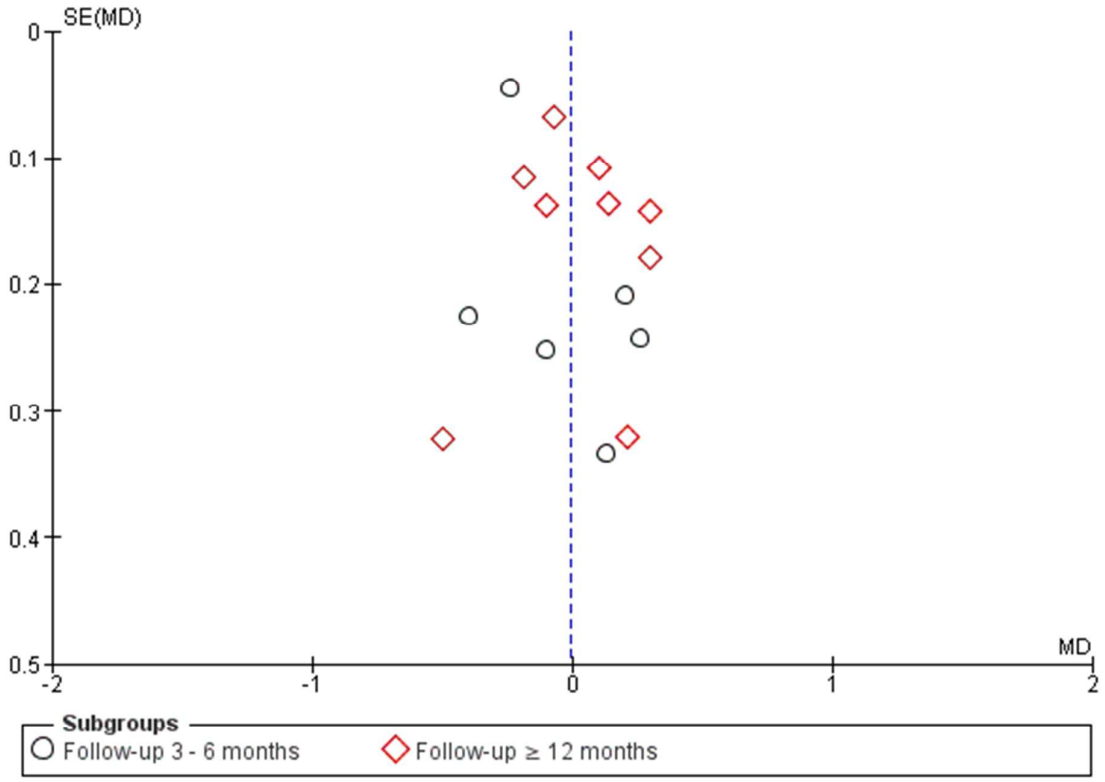
Body weight



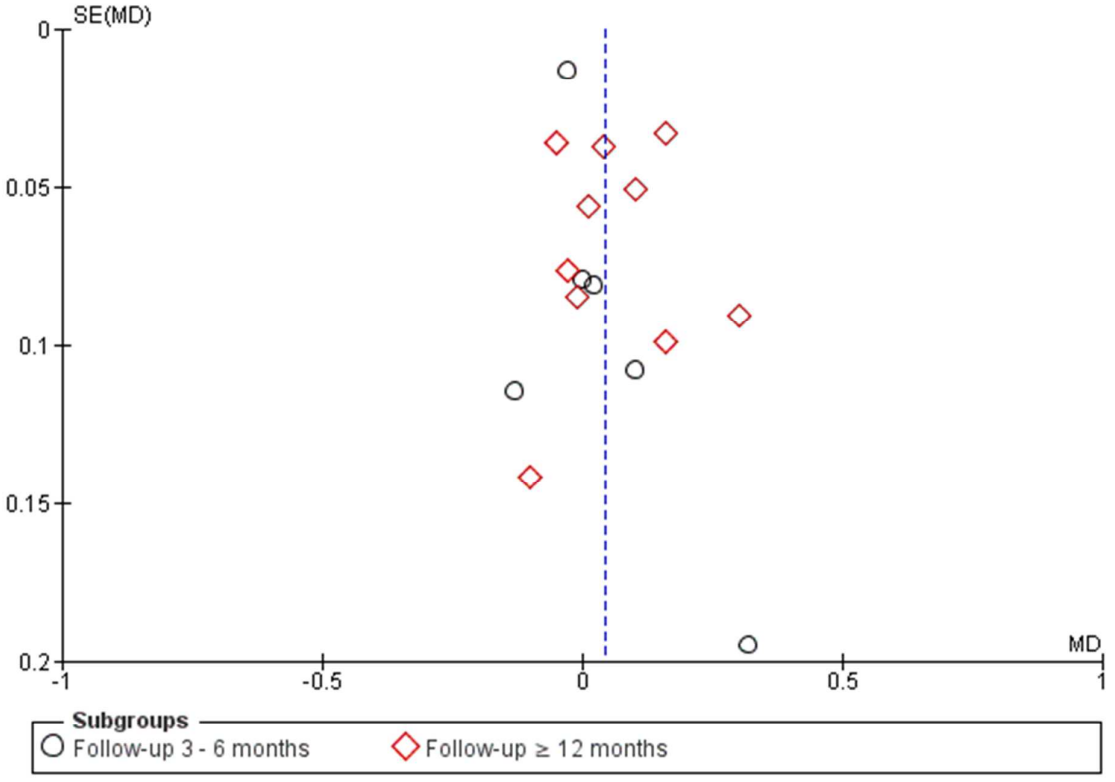

HbA1c



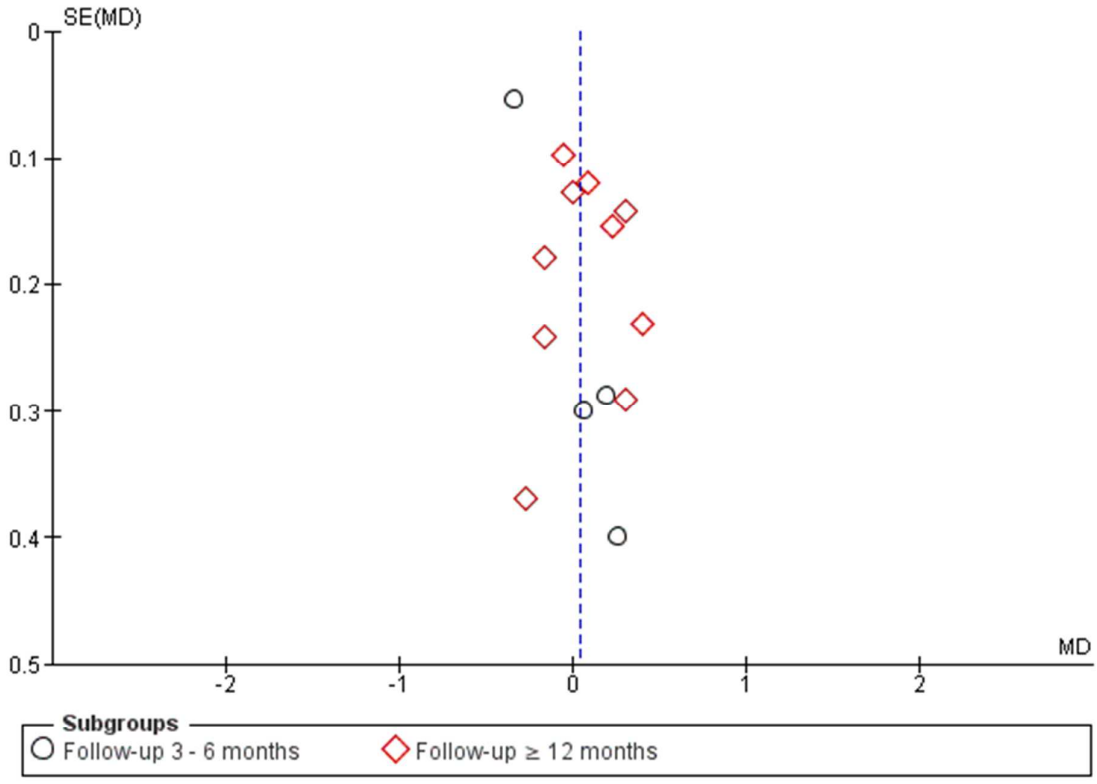
LDL-cholesterol



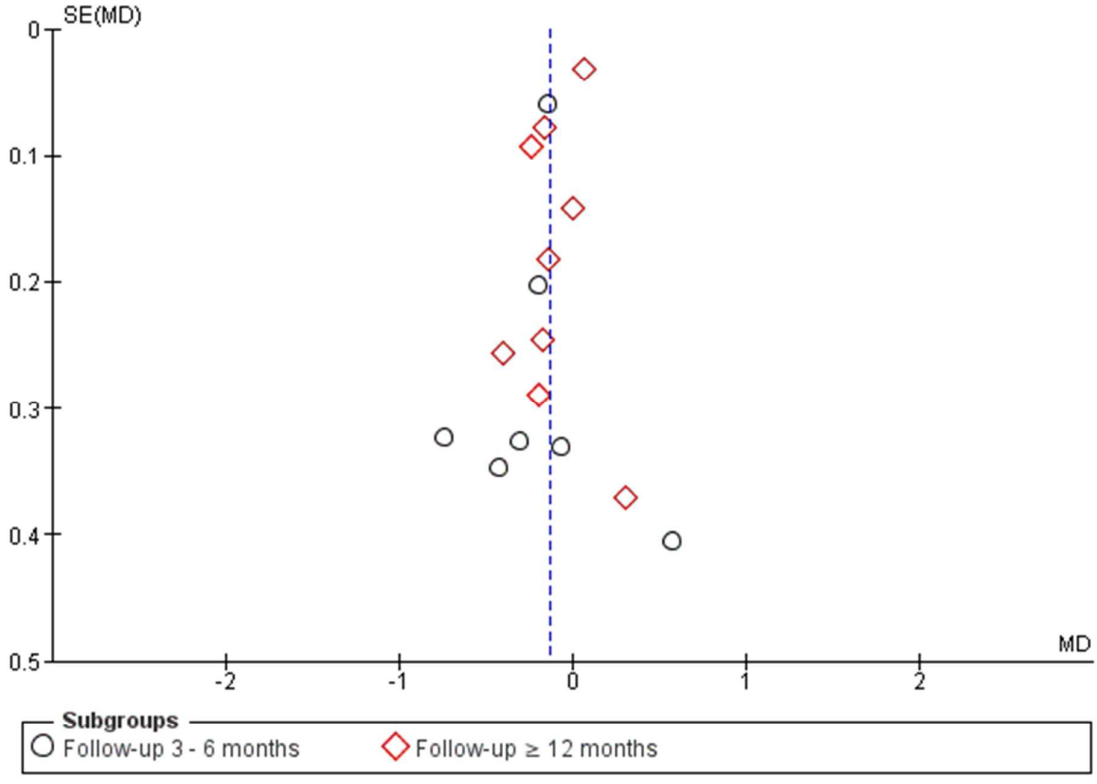

HDL-Cholesterol



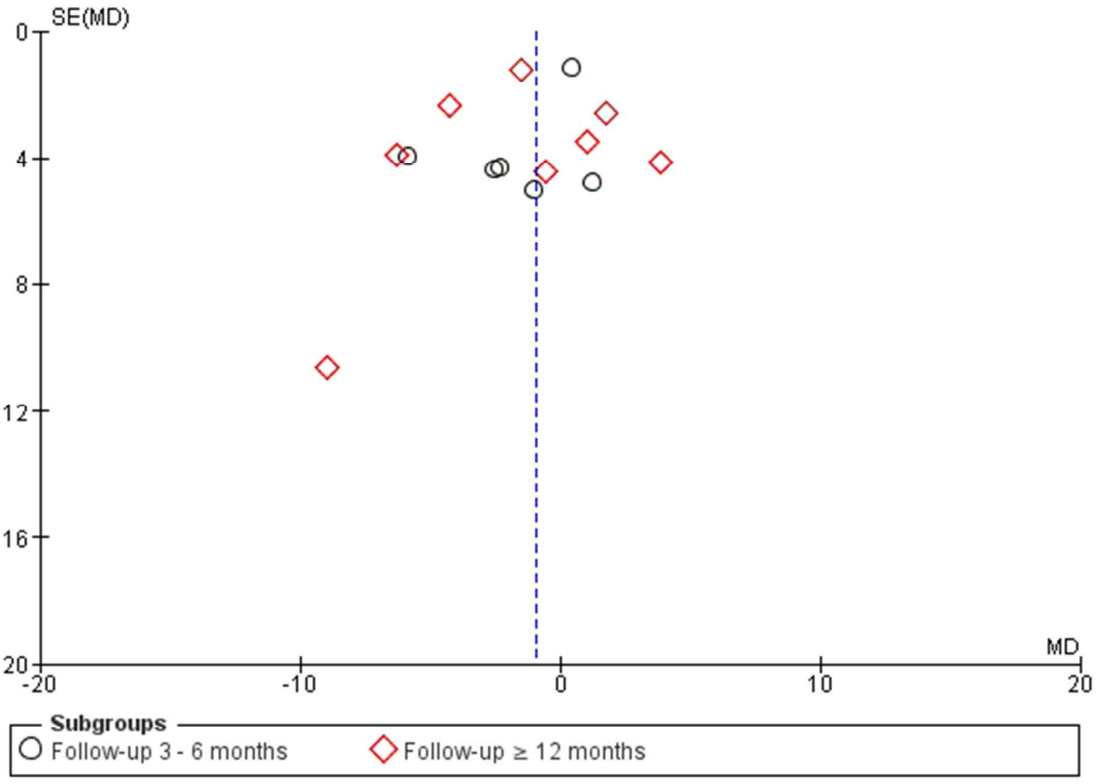
Total cholesterol



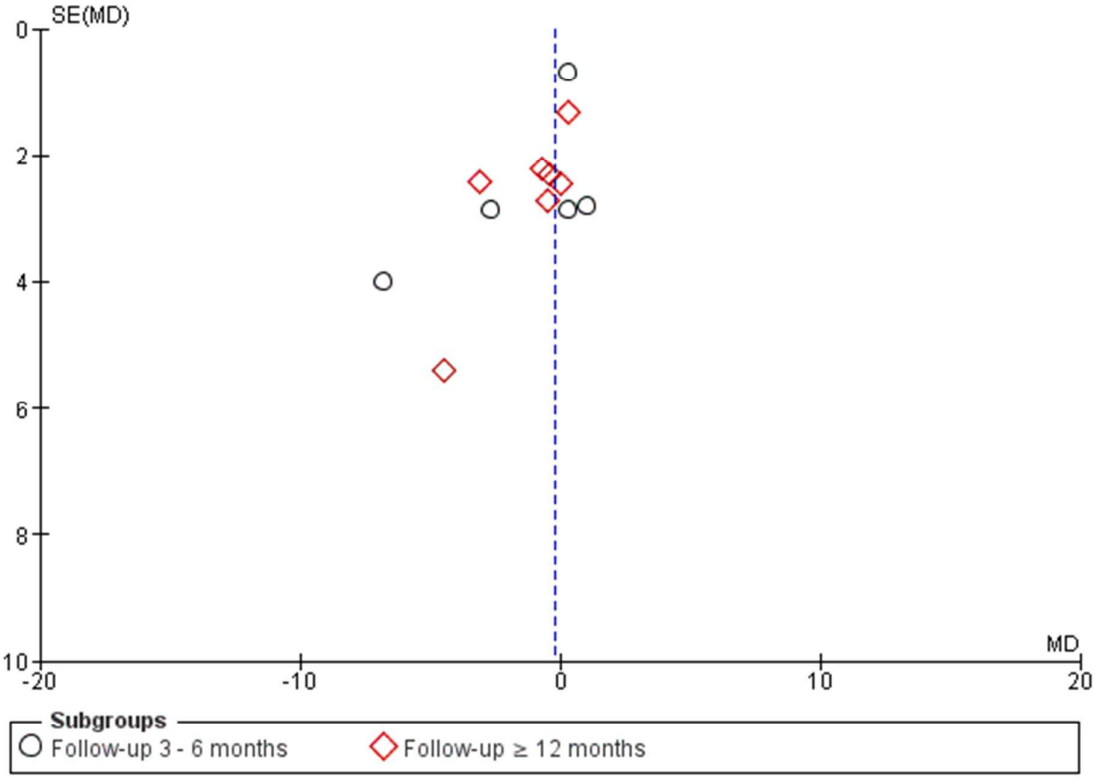

Triacylglyserols



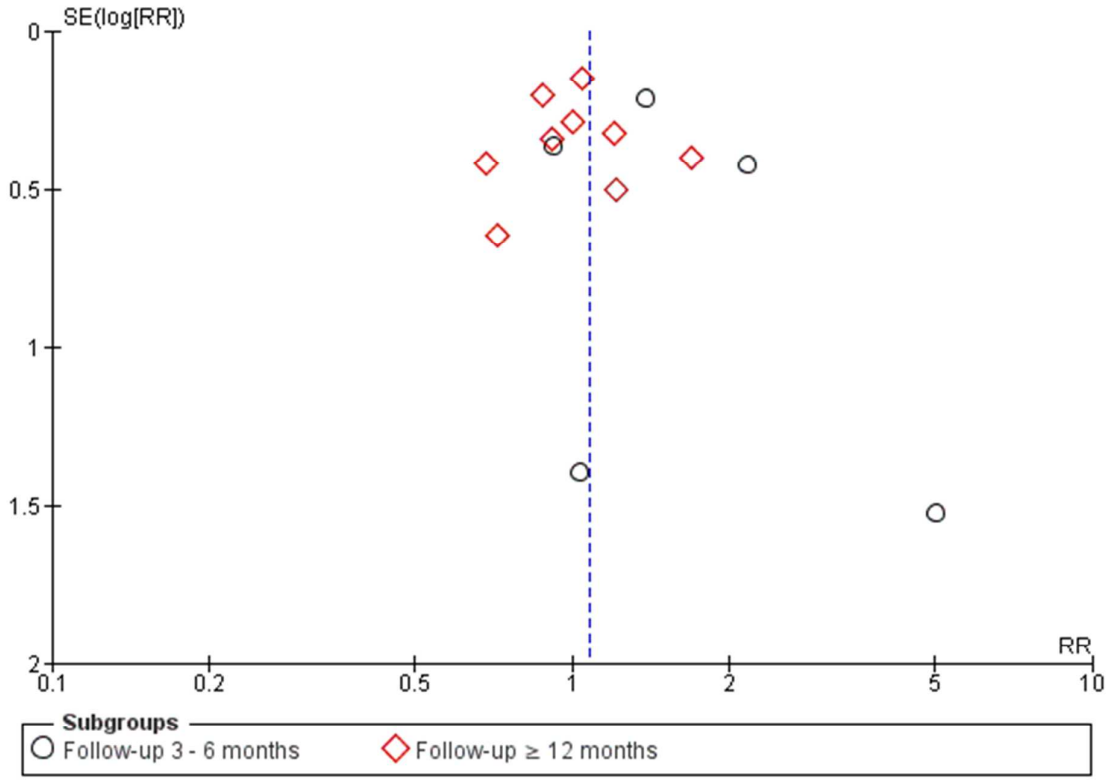
Systolic blood pressure




Diastolic blood pressure



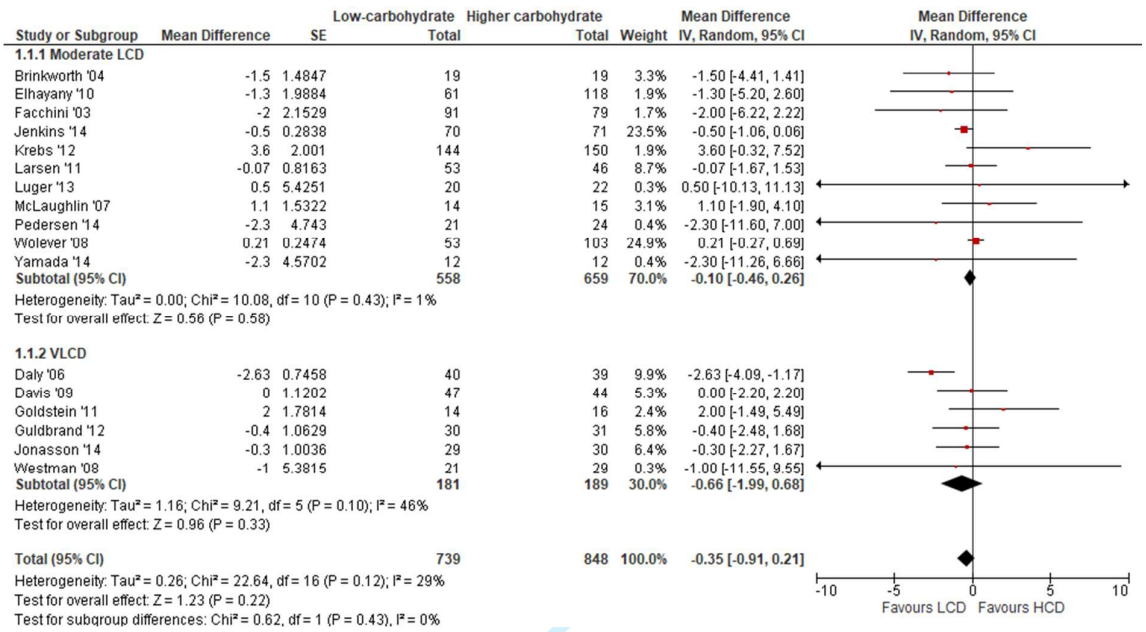
Compliance



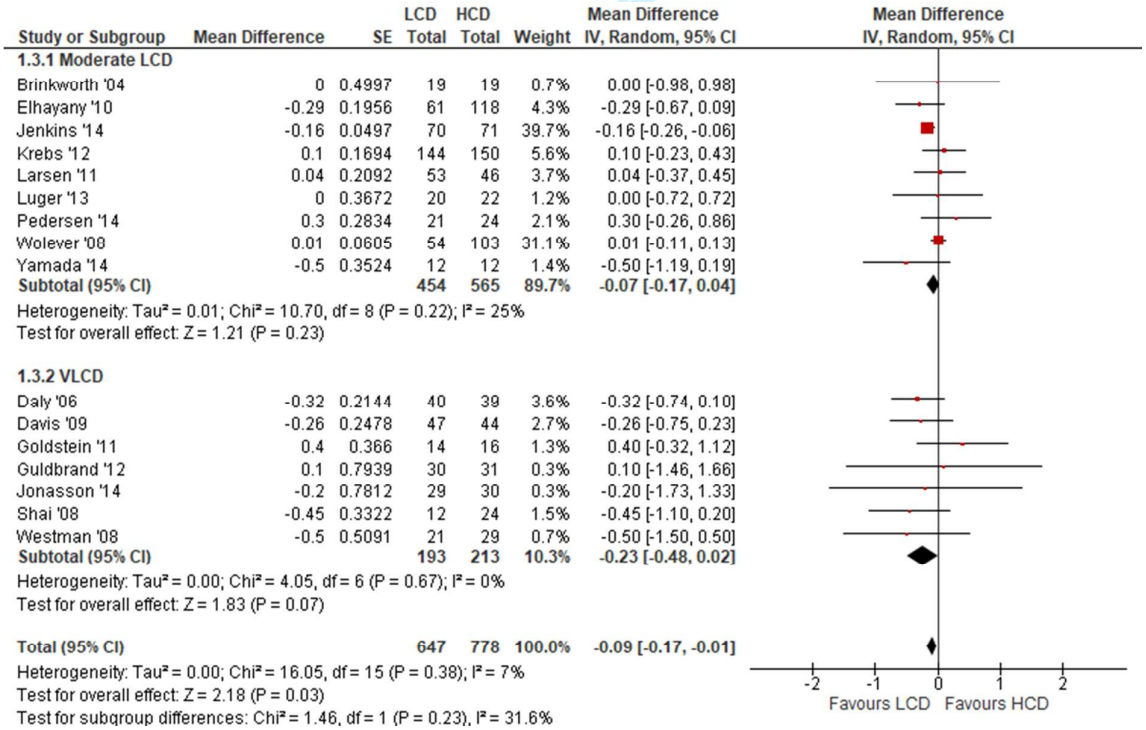
## Supplementary figure 3

Subgroup analysis based on carbohydrate restriction in the LCD group (moderate LCD: 30-40% TE CHO and VLCD: 21-70 g CHO)

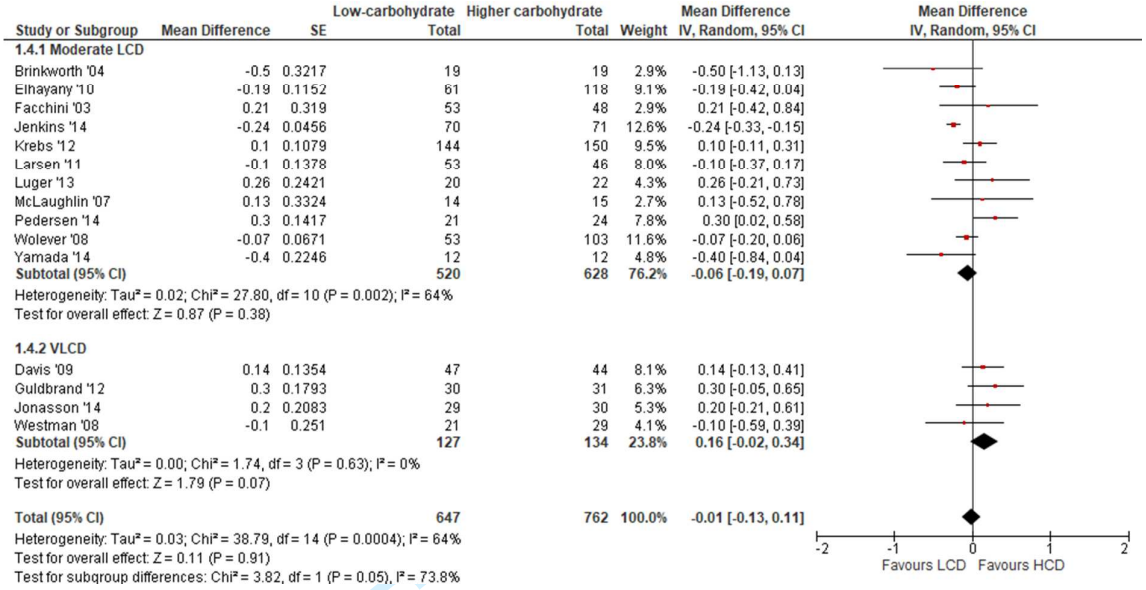
*Body weight*



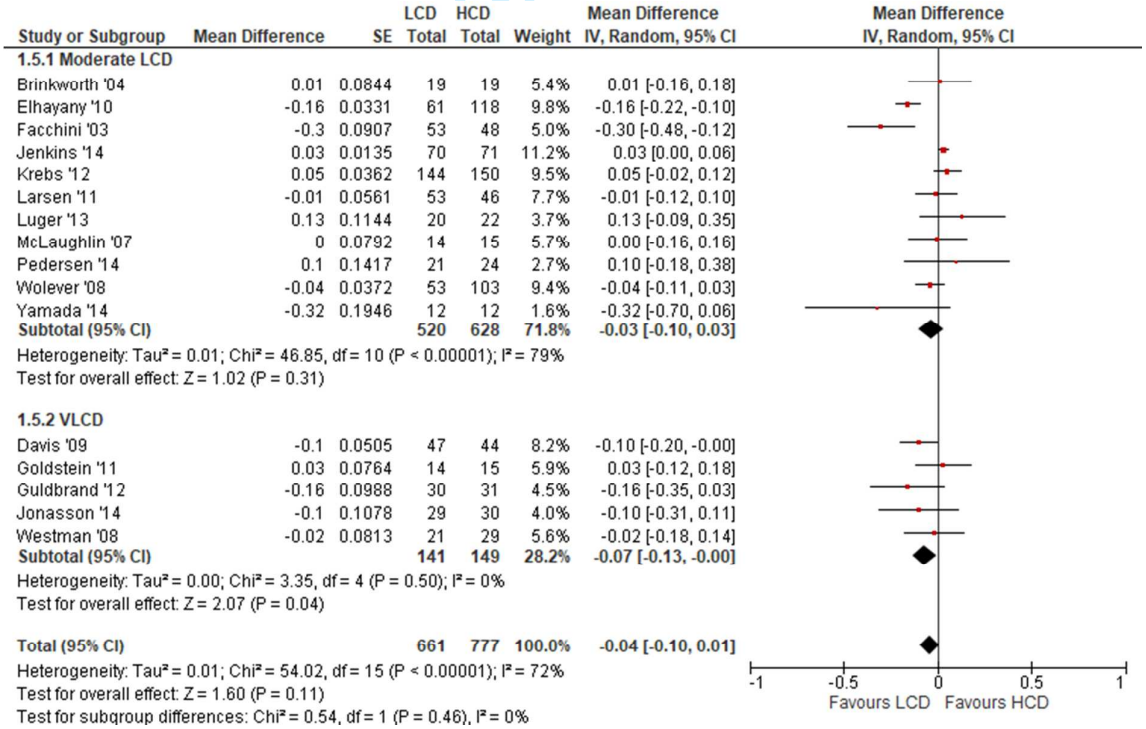

*Hb1Ac*



*LDL-cholesterol*

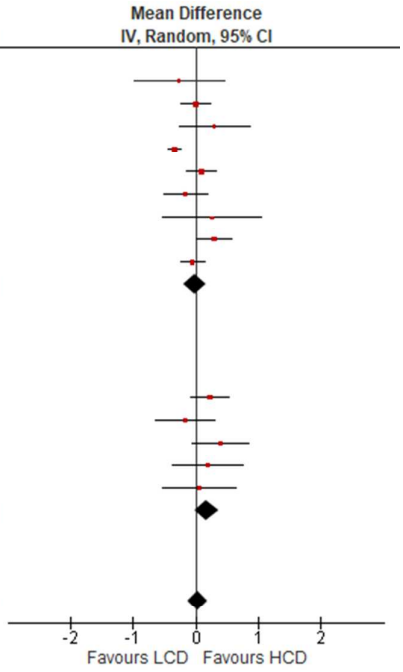



*HDL-cholesterol*



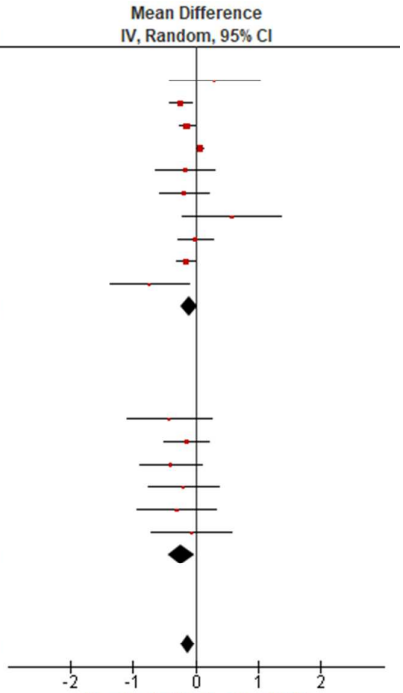
*Total cholesterol*

| Study or Subgroup | Mean Difference | SE | LCD Total | HCD Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 Moderate LCD** | | | | | | |
| Brinkworth '04 | -0.27 | 0.3685 | 19 | 19 | 3.5% | -0.27 [-0.99, 0.45] |
| Elhayany '10 | 0 | 0.1265 | 61 | 118 | 9.5% | 0.00 [-0.25, 0.25] |
| Facchini '03 | 0.3 | 0.2896 | 53 | 48 | 4.8% | 0.30 [-0.27, 0.87] |
| Jenkins '14 | -0.34 | 0.054 | 70 | 71 | 11.8% | -0.34 [-0.45, -0.23] |
| Krebs '12 | 0.09 | 0.1196 | 144 | 150 | 9.8% | 0.09 [-0.14, 0.32] |
| Larsen '11 | -0.16 | 0.1786 | 53 | 46 | 7.8% | -0.16 [-0.51, 0.19] |
| McLaughlin '07 | 0.26 | 0.3984 | 14 | 15 | 3.1% | 0.26 [-0.52, 1.04] |
| Pedersen '14 | 0.3 | 0.1417 | 21 | 24 | 9.0% | 0.30 [0.02, 0.58] |
| Wolever '08 | -0.05 | 0.0975 | 53 | 103 | 10.5% | -0.05 [-0.24, 0.14] |
| **Subtotal (95% CI)** | | | **488** | **594** | **69.8%** | **-0.01 [-0.20, 0.17]** |
| Heterogeneity: Tau² = 0.05; Chi² = 32.53, df = 8 (P < 0.0001); I² = 75% | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | |
| **1.6.2 VLCD** | | | | | | |
| Davis '09 | 0.23 | 0.1531 | 47 | 44 | 8.6% | 0.23 [-0.07, 0.53] |
| Goldstein '11 | -0.16 | 0.2417 | 14 | 16 | 5.9% | -0.16 [-0.63, 0.31] |
| Guldbrand '12 | 0.4 | 0.2305 | 30 | 31 | 6.2% | 0.40 [-0.05, 0.85] |
| Jonasson '14 | 0.2 | 0.2865 | 29 | 30 | 4.9% | 0.20 [-0.36, 0.76] |
| Westman '08 | 0.06 | 0.2987 | 21 | 29 | 4.6% | 0.06 [-0.53, 0.65] |
| **Subtotal (95% CI)** | | | **141** | **150** | **30.2%** | **0.17 [-0.02, 0.37]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.16, df = 4 (P = 0.53); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.08) | | | | | | |
| **Total (95% CI)** | | | **629** | **744** | **100.0%** | **0.04 [-0.12, 0.20]** |
| Heterogeneity: Tau² = 0.05; Chi² = 44.94, df = 13 (P < 0.0001); I² = 71% | | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | | |
| Test for subgroup differences: Chi² = 1.84, df = 1 (P = 0.17), I² = 45.7% | | | | | | |

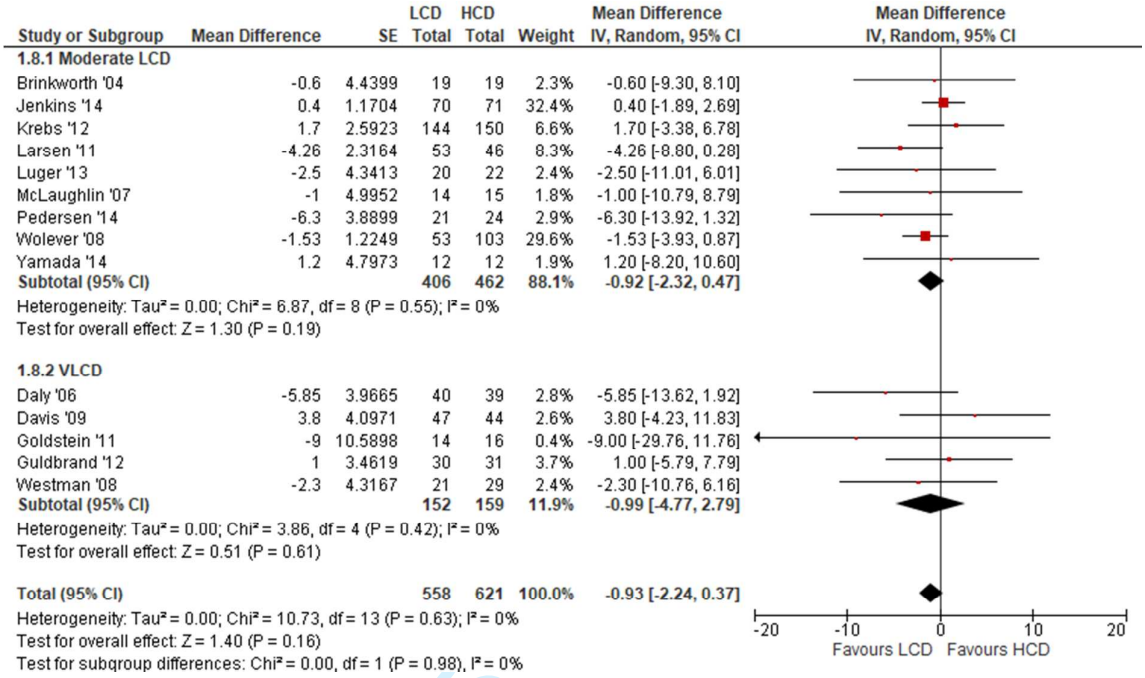



*Triacylglycerol*

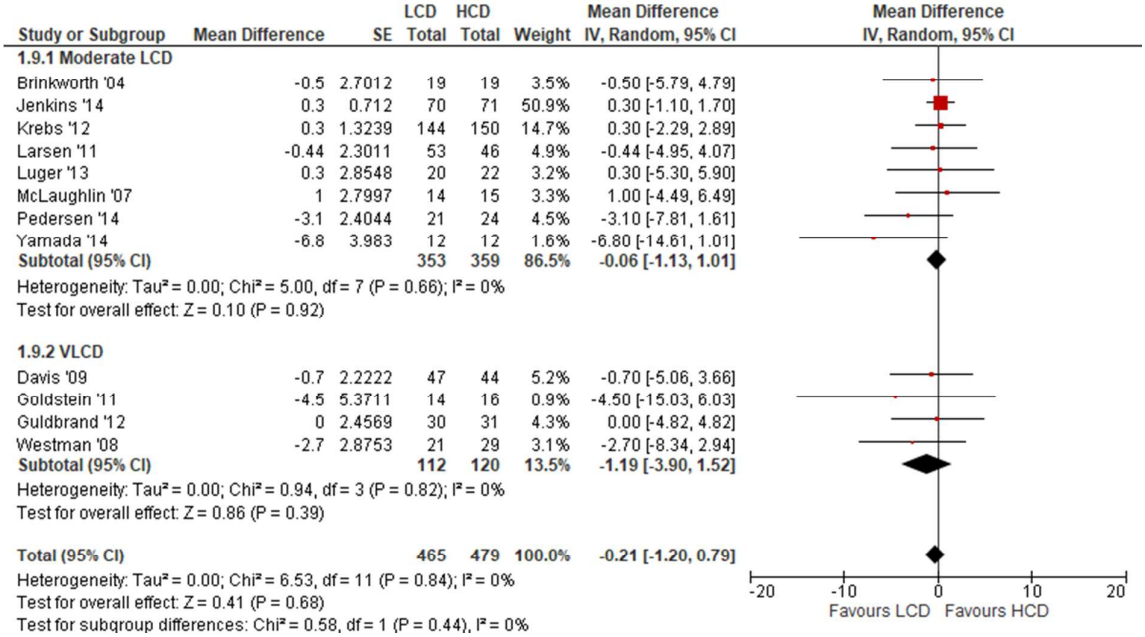
| Study or Subgroup | Mean Difference | SE | LCD Total | HCD Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.7.1 Moderate LCD** | | | | | | |
| Brinkworth '04 | 0.3 | 0.3707 | 19 | 19 | 2.0% | 0.30 [-0.43, 1.03] |
| Elhayany '10 | -0.24 | 0.0924 | 61 | 118 | 11.8% | -0.24 [-0.42, -0.06] |
| Jenkins '14 | -0.14 | 0.0608 | 70 | 71 | 14.5% | -0.14 [-0.26, -0.02] |
| Krebs '12 | 0.07 | 0.0321 | 144 | 150 | 16.6% | 0.07 [0.01, 0.13] |
| Larsen '11 | -0.17 | 0.2449 | 53 | 46 | 4.0% | -0.17 [-0.65, 0.31] |
| Luger '13 | -0.19 | 0.2021 | 20 | 22 | 5.3% | -0.19 [-0.59, 0.21] |
| McLaughlin '07 | 0.58 | 0.4043 | 14 | 15 | 1.7% | 0.58 [-0.21, 1.37] |
| Pedersen '14 | 0 | 0.1417 | 21 | 24 | 8.2% | 0.00 [-0.28, 0.28] |
| Wolever '08 | -0.16 | 0.0786 | 53 | 103 | 13.0% | -0.16 [-0.31, -0.01] |
| Yamada '14 | -0.74 | 0.323 | 12 | 12 | 2.6% | -0.74 [-1.37, -0.11] |
| **Subtotal (95% CI)** | | | **467** | **580** | **79.8%** | **-0.10 [-0.23, 0.03]** |
| Heterogeneity: Tau² = 0.02; Chi² = 29.62, df = 9 (P = 0.0005); I² = 70% | | | | | | |
| Test for overall effect: Z = 1.49 (P = 0.14) | | | | | | |
| **1.7.2 VLCD** | | | | | | |
| Daly '06 | -0.42 | 0.3462 | 40 | 39 | 2.3% | -0.42 [-1.10, 0.26] |
| Davis '09 | -0.14 | 0.1824 | 47 | 44 | 6.1% | -0.14 [-0.50, 0.22] |
| Goldstein '11 | -0.4 | 0.2555 | 14 | 16 | 3.8% | -0.40 [-0.90, 0.10] |
| Guldbrand '12 | -0.2 | 0.2884 | 18 | 17 | 3.1% | -0.20 [-0.77, 0.37] |
| Jonasson '14 | -0.3 | 0.3256 | 29 | 30 | 2.5% | -0.30 [-0.94, 0.34] |
| Westman '08 | -0.06 | 0.3295 | 21 | 29 | 2.5% | -0.06 [-0.71, 0.59] |
| **Subtotal (95% CI)** | | | **169** | **175** | **20.2%** | **-0.23 [-0.45, -0.02]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 5 (P = 0.93); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.14 (P = 0.03) | | | | | | |
| **Total (95% CI)** | | | **636** | **755** | **100.0%** | **-0.13 [-0.24, -0.02]** |
| Heterogeneity: Tau² = 0.02; Chi² = 34.55, df = 15 (P = 0.003); I² = 57% | | | | | | |
| Test for overall effect: Z = 2.26 (P = 0.02) | | | | | | |
| Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² = 10.1% | | | | | | |



*Systolic blood pressure*




*Diastolic blood pressure*



*Attrition rate*