Effects of low carbohydrate versus low fat diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments

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Short running head: Low carbohydrate diet versus low fat diet for DM2

Abbreviations: DM2, type 2 diabetes mellitus; CCT, controlled clinical trial; en%, energy percentage; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, haemoglobin A1c (glycated haemoglobin); MD, mean difference; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial

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ABSTRACT

Background: It remains uncertain which diet is best for people with type 2 diabetes mellitus (DM2).

Objective: We compared the effects of dietary carbohydrate- versus fat restriction on markers of metabolic syndrome and quality of life in people with DM2.

Design: This systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), compares the effects of a low carbohydrate (≤ 40 en%) diet versus those of a low fat (≤ 30 en%) diet over a period of at least four weeks in patients with DM2. Two investigators independently selected studies, extracted data and assessed risk of bias. The GRADE approach was used to assess the certainty of evidence. Pooled mean differences and 95% confidence intervals were calculated using a random effects model.

Results: Thirty-three RCTs and 3 CCTs (n = 2161) were included. HbA1c declined more in people using low carbohydrate food than in those on low fat food in the short term (mean difference (MD) -1.38%, 95% CI: -2.64, -0.11; very low certainty evidence). At one year, the MD was reduced to -0.36% (95% CI:-0.58, -0.14; low certainty evidence), at two years the difference had disappeared. There is low to high (majority moderate) certainty for small improvements of unclear clinical importance in plasma glucose, triglycerides and HDL concentrations favoring low carbohydrate food at half of the pre-specified time points. There was little to no difference in LDL concentration or any of the secondary outcomes (bodyweight, waist circumference, blood pressure, quality of life) in response to either diet (very low to high certainty evidence).

CONCLUSION

Currently available data provide low to moderate certainty evidence that dietary carbohydrate restriction to a maximum of 40 en% yields slightly better metabolic control of uncertain clinical importance than reduction of fat to a maximum of 30 en% in people with DM2.

Keywords: Diabetes, low carbohydrate diet, low fat diet, HbA1c, GRADE

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a multifactorial disease, emanating from gene-environment interactions (1). Diet quality and quantity are at the heart of its pathogenesis (2). Although it is quite clear that nutrition plays a pivotal role in the pathogenesis of DM2, it remains unclear which dietary measures are most effective in ameliorating metabolic derangements. There is little doubt however, that reduction of body fat stores dampens chronic inflammation and improves metabolic anomalies. Thus, it is perhaps unsurprising to note that dietary guidelines for DM2 tend to focus on weight loss as a primary goal. In this context, the consumption of low fat food has been advocated for many years, inspired by at least two assumptions. Firstly, that because fat contains more calories per gram, eating less fat will reduce fat stores more than restricting protein or carbohydrate intake; and secondly, that consumption of (saturated) fat is associated with dyslipidemia (elevated low density lipoprotein cholesterol concentrations) and cardiovascular disease, and the main complications of diabetes mellitus all relate to vascular obstruction. However, the most recent clinical guideline recommendations conclude that “as there is no single ideal dietary distribution among carbohydrates, fats and proteins for people with diabetes, distribution should be individualized while keeping total calories and metabolic goals in mind” (3). This conclusion has been challenged in a number of reports, which claim that restriction of carbohydrates, and in particular refined carbohydrates, is most effective in redressing metabolic anomalies in DM2 (4-6). This position concurs with common sense, as carbohydrates are the only (direct) source of glucose in the diet. It goes without saying that dietary restriction of sugar and starch (chains of glucose monomers linked by glycosidic bonds) is therefore expected to lower blood glucose peaks. Moreover, as any excess glucose is readily converted into (saturated) fat by hepatic de novo lipogenesis and subsequently secreted as very low density triglycerides (7), restriction of starchy food is expected to reduce plasma triglyceride levels. However, none of

the available reports, which include several systematic reviews, specifically compared the impact of low carbohydrate diets with that of low fat diets on glucose control, bodyweight and plasma lipid profiles in people with DM2. Indeed, the majority of these compared the effects of carbohydrate restricted versus unrestricted diets, which increases the possibility of imbalanced energy content of comparator diets (see Discussion). We present the results of a systematic review and meta-analysis of available data comparing the effects of low carbohydrate *versus* low fat dietary interventions on glucose control and other important metabolic and anthropometric parameters, as well as on quality of life in individuals with DM2. Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology was used to rate the certainty of the evidence (8).

METHODS

This systematic review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (9) and in concordance with the corresponding prospectively registered protocol in PROSPERO (CRD42017052467)(10).

Eligibility criteria

We included randomized controlled trials (RCTs) and controlled clinical trials (CCTs), which compared a low carbohydrate diet *versus* a low fat diet over a period of at least four weeks in adult patients (age ≥18) with DM2. A low carbohydrate diet was defined as any dietary intervention containing 40 energy percentage (en%) or less of carbohydrate, and a low fat diet as one containing 30 energy percentage (en%) or less of fat. The 40 en% of carbohydrate was chosen as the upper limit for inclusion, because this represents the most common minimum carbohydrate intake at a global level (12). Studies that stated clearly, in the methods section, their intention to meet these cut-off values of energy percentages were eligible for inclusion. However, if the actual intake of any one of the macronutrients exceeded 2 en% above these

limits, these data were not included in the final analysis. We also only included data from cross-over trials which had incorporated wash-out periods of at least four weeks between interventions. In the absence of an adequate wash-out period, we used the data from these trials only if we were able to extract the relevant data for the first phase (i.e., prior to the crossover), because we considered the risk of carryover effects to be prohibitive. We excluded studies which had included people suffering from other chronic diseases except for hypertension or cardiovascular disease. Studies were also excluded if they included participants who were using systemic corticosteroids, were suffering from any (progressive) disease requiring hospital care, from an eating disorder or any other disease necessitating special dietary requirements (except sodium restriction).

Literature search

All the search strategies for the various databases (**Supplemental Table 1**) were designed and tested by a medical research librarian. The searches included the following databases: Medline, PubMed, Embase, Web of Science, Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), Emcare, Academic Search Premier, ScienceDirect, Latin American and Caribbean Health Science Information database (LILACS) and Índice Bibliográfico Español en Ciencias de Salud (IBECS) and covered the period from inception up to 21 March 2017. Additional searches were conducted in the following trials registers (www.isrctn.com/, www.clinicaltrials.gov, www.anzctr.au, apps.who.int/trialsearch/, www.clinicaltrialsregister.eu). Two review authors (EvZ and ZF) also examined the bibliographies of the included and excluded studies and the Public Health Collaboration database (https://phcuk.org/rcts/) for further references to potentially eligible studies. Finally, we checked the bibliographic reference lists of previous systematic reviews which had covered this clinical topic.

Study selection

Two authors (EvZ and ZF) independently assessed the titles and abstracts of studies identified from the searches and, if necessary, obtained and reviewed the full text versions to establish whether they met the inclusion criteria. Any disagreements on eligibility were resolved through discussion to reach consensus and, when necessary, by involving a third author (HP). Studies that did not meet our inclusion criteria were excluded. The number of reports retrieved, the number of included and excluded studies and the reasons for their exclusion are presented in a flow diagram (**Figure 1**).

Data extraction and risk of bias assessment

Two authors (EvZ and ZF) independently collected study details and outcomes data using a piloted data extraction form and any disagreements on data entry were resolved through discussion or by consultation with a third author (HP). We extracted study characteristics (design, year of publication, setting, country of origin, duration of intervention and follow-up), and patients' characteristics (sample size, gender, age, inclusion and exclusion criteria, number of drop-outs and reasons for loss to follow-up, baseline data, medication for diabetes). Key details were extracted of the diet (en% of carbohydrates, protein and fat, program support measures and degree of compliance, targeted intake and actual intake, whether diets were isocaloric, aimed at weight maintenance or weight loss), exercise, our prespecified primary and secondary outcomes, and information on funding and declarations of interest. The trial investigators and sponsors of included studies that were less than 10 years old were contacted for additional trial details and missing data.

Our primary outcomes were change from baseline of: HbA1c concentration in whole blood, and plasma glucose, triglyceride, HDL and LDL cholesterol concentrations in fasting condition. Our secondary outcomes were change from baseline of: body weight, body mass

index (BMI), waist circumference, blood pressure and quality of life. We grouped data in short term measurements (up to 8 weeks), medium low term (≥ 8-16 weeks), medium high term (≥ 16-26 weeks), and long term (> 26 weeks).

Two review authors (EvZ and ZF) independently assessed the risk of bias for each RCT, using the Cochrane Collaboration's domain based assessment tool (11). Inconsistencies in judgements were resolved through discussion or by involving a third author (HP). The overall risk of bias for each study was determined as follows: Low risk of bias when all domains were assessed as low risk (plausible bias unlikely to seriously alter the results). Unclear risk of bias when at least one domain was classified as unclear risk (plausible bias that raises some doubt about the results). High risk of bias when at least one domain was judged as at high risk (plausible bias that seriously weakens confidence in the results). For non-randomized controlled trials we used ROBINS-I (seven domain tool) to assess the risk of bias (13). An overall risk of bias was assigned based on the assessment of each domain as low, moderate, serious, or critical, with the minimum overall risk typically determined by the highest risk assigned in any individual domain.

Statistical analysis

All of the prespecified outcomes for this systematic review were only reported as continuous data, for which we calculated the mean differences (MD) with their associated 95% confidence interval (CI), and carried out a complete case analysis if data were missing or incomplete. Heterogeneity between the studies in effect measures was assessed using the I^2 statistic with an I^2 value greater than 50% indicative of substantial heterogeneity. We combined studies which evaluated similar outcomes and pooled their data in a meta-analysis independently of the observed heterogeneity. Following the recommendations of the Grading of Recommendations Assessment, Development and Evaluation working group we

considered downgrading the certainty of evidence for inconsistency when I^2 exceeded 50%, whilst taking other considerations for downgrading into account (8). We intended assessing publication bias based on the recommendations on testing for funnel plot asymmetry (14), but the paucity of studies evaluating any of the outcomes at the same specific time points did not permit such an assessment. The lack of an adequate number of included studies reporting on the subgroups specified in our protocol, precluded any attempts to carry out our planned subgroup analyses.

The data reported for our predefined outcomes were pooled where possible using a random-effects model and presented in forest plots. All analyses were undertaken using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

To explore sources of statistical heterogeneity between studies and assess the robustness of our data we have conducted several sensitivity analyses. We repeated our analyses using the fixed-effects model to enable an assessment of the influence of small-study effects on the results of any of the meta-analyses in which there was evidence of between study heterogeneity ($I^2 > 0\%$)(see **Supplemental Figure 1**). We also undertook sensitivity analyses to examine the effect of excluding studies at overall high risk of bias (see **Supplemental Figure 2**) and the impact of excluding studies that were the cause of substantial heterogeneity (see **Supplemental Figure 3**).

Certainty of evidence

We applied the GRADE approach using GRADEproGDT (http://gradepro.org) to assess the certainty of evidence for the predefined outcomes as presented in the Summary of Findings Tables (8). This approach takes into consideration: study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision and publication bias. Two authors (EvZ and TK) independently rated the certainty of evidence for the prespecified

outcomes as ‘high’, ‘moderate’, ‘low’ and ‘very low, and discrepancies were resolved by consensus or with input from a third author (ZF or HP).

RESULTS

Search results

Our searches across the databases identified 993 articles and 91 further references to abstracts. Nine additional records were found through other resources and hand searching and we also identified nine ongoing trials (Figure 1). After examination of the titles and abstracts and the removal of any duplicate publications, we excluded 950 references. A total of 138 full-text copies were obtained for further evaluation. Of these we excluded nine ongoing studies, which had not published any data, 46 studies which were co-publications (studies that have been published more than once, or had evaluated other outcomes from the same study population). We also excluded 47 studies (15-61) for other reasons, the most important of which were that the composition of the diets did not meet our inclusion criteria (i.e. the pre-specified cut-off values), or that the actual intake during the study appeared to be higher than the agreed or prescribed percentages of carbohydrates or fat (or both). Other reasons for exclusion were that studies did not appear to have been conducted in patients with DM2, that there were insufficient details reported on the content of the diets, or that the study duration was too short. For fuller details see **Supplemental Table 2-5**.

Study characteristics

Thirty-six studies (33 RCTs and three CCTs), which had evaluated a total of 2161 patients, were included in this systematic review (62-97). **Table 1** summarizes the key characteristics of these studies. **Supplemental Table 6** provides more detailed information on the 36 studies as well as the specific judgements per risk of bias domain for each study. Four studies included only men, three only women and the remainder included both men and women in

varying proportions. Samples sizes were rather small (ranging from less than 20 to 60 patients) in most of the studies, with just eight studies evaluating more than 100 patients (66-68,76,86,89,93,96). The mean age of participants was 56.6 years, and was consistent across the studies (mean range 32 to 65 years, majority between 50 and 60 years). A majority of the studies had a two-arm design (n = 31), and the remainder were three-arm studies (n = 4) and one four-arm study. Most of the studies were conducted in Europe (n = 14) or in the US and Canada (n = 15). One study was conducted in Mexico, two in Israel, two in Japan and a further two in Australia. Study duration varied from four weeks extending to seven years in one outlying study, with an overall mean period of 33 weeks (exclusion of the outlier would provide a more representative mean of 24 weeks). A total of 19 studies were conducted before 2000, and the remaining 17 after the year 2000.

In nine of the studies the meals were provided by the hospital or were home delivered, or patients were hospitalized throughout the study (62,64,65,69-71,81,84,88). In the other studies patients underwent specific training by a dietitian, were provided with a list of foods to be consumed, and received regular follow-up sessions (phone calls, hospital visits) to ensure adherence to the dietary recommendations.

Eight of the studies encouraged an increase in physical activity by participants during the study period (66,68,72,76,81,83,87,93). The study of Bozzetto et al (63), which examined the effects of diet-exercise interaction, included a mandatory supervised exercise program in two of the four arms, but we only included data from the arms without exercise as the focus of this systematic review was a specific comparison of dietary interventions.

In 16 studies the diets were isocaloric (62-64,68-71,73,81,85,88,90,91,93-95). Nine studies aimed for weight reduction by calorie restriction in both diets (66,68,72-75,81,83,93) and in

two studies (89,97) just one of the diets was calorie restricted. In eight studies the calorie intake was adjusted to maintain constant body weight (62-65,70,84,88,95).

The review included 17 cross-over trials and in 14 there was no washout, or the washout period was less than four weeks, which we considered too short to exclude potential carry-over effects. As there were no data reported separately for each phase (data were combined for both phases), we were unable to use these 14 studies, although they matched our inclusion criteria (see Supplemental Table 4)(62,64,65,69-71,77,80,85,88,90-92,95). The metabolic effects of dietary interventions can persist for a variable length of time (depending on the nature of the intervention), and the carry-over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. The three remaining cross-over studies had a washout of at least four weeks and provided data which we were able to include in the meta-analyses (78,84,94).

The data from five of the RCTs were unusable (see Supplemental Table 4). One study (79) did not address any of our outcomes, one study (82) did not provide separate data for DM1 and DM2 patients, three other studies (76,86,87) targeted our criteria of a low carbohydrate versus low fat diet (en%), but appeared to subsequently exceed our cut-off values by more than 2 en% at follow-up. Furthermore, in the study of Samaha et al data are reported on some outcomes for diabetics (glucose, insulin and Hb1Ac), but it is unclear how many diabetic patients remained in each intervention group throughout the study period (86). The report indicated that there was a 40% drop out but also failed to clarify how many diabetics dropped out in each intervention group, which did not permit further analysis of the data. Overall, out of the 36 included studies only 17 provided data which could be further analyzed and subsequently entered into the meta-analyses.

Our predefined outcomes were evaluated as follows: HbA1c (25 studies); plasma concentration in fasting condition: glucose (29 studies), triglycerides (31 studies), HDL-cholesterol (30 studies), LDL-cholesterol (28 studies); body weight (23 studies), BMI (10 studies), waist circumference (seven studies), blood pressure (11 studies) and quality of life (five studies).

Sources of funding were reported in all but two of the studies (78,97). Declarations of conflicts of interest were only reported in four studies (72,74,87,96), but we considered that either funding or conflicts of interest might have resulted in potential bias in six (72,75,90-92,96) of the studies, where the Sugar Foundation, Mars, or other food industry provided funding for the study or the investigators received honoraria from these entities.

Risk of bias assessment

The risk of bias assessments for the 33 included RCTs are presented in **Figure 2**. We were successful in contacting trialists and clarifying trial details and subsequently amending our judgements in several of the risk of bias domains for three studies (63,66,94). We further categorized the overall risk of bias for the 33 studies, 19 of which were judged to be at high risk of bias, and the remaining 14 studies at unclear risk of bias. The most important reasons why studies were considered at high risk of bias was the lack of a washout period (or too short washout period) between diets in the cross-over studies (n = 13), and/or a high drop-out rate (n = 8) and one study (68) appeared to be quasi randomized. See Table 1 for summarized assessments of Risk of Bias and Supplemental Table 6 for detailed risk of bias judgements.

The risk of bias assessments for the three controlled clinical trials (CCTs)(70,74,83) are shown separately in **Table 2**. The overall risk of bias in these studies varied from moderate to serious risk of bias.

Outcomes

Sensitivity analyses were carried out for our meta-analyses where applicable and are presented for our prespecified outcomes in Supplemental Figure 1-3 (see also under statistical analyses above). The robustness of our results was underpinned by the minimal divergence in effect estimates between our meta-analyses and the sensitivity analyses, which at no stage reached a clinically important difference.

Change from baseline of glycated hemoglobin (HbA1c)

This outcome was assessed and reported in 14 studies some of which provided data within several measurement time points (63,66-68,72,73,78,83,84,89,93,94,96,97). In contrast with low fat diets, low carbohydrate diets improved HbA1c at almost all time points, but the difference diminished over time, which is unremarkable in view of the well acknowledged difficulties of adherence to dietary changes over extended periods of time (see **Figure 3**) (very low to moderate certainty evidence).

Change from baseline of fasting plasma glucose concentration

Data for this outcome were provided by 14 studies (63,67,68,72,74,75,78,81,83,89,93,94,96,97). See **Figure 4**. In two time windows, the low carbohydrate diets induced a greater decrease of fasting glucose concentration than the low fat diets (≥8-16 weeks and ≥16-26 weeks) (moderate certainty evidence).

Change from baseline of fasting triglycerides concentration

Fifteen studies evaluated triglycerides in the fasting condition (63,66-68,72-75,78,81,84,93,94,96,97). See **Figure 5**. Although there was a trend towards effect in favor of the low carbohydrate data, only the data reported beyond 16 weeks favored the low carbohydrate diets indeed (moderate to high certainty evidence).

Change from baseline of fasting HDL cholesterol concentration

This outcome was assessed in 12 studies (63,66,68,72-74,78,81,84,93,94,96). See **Figure 6**. The pooled data at several time points showed an increase in HDL in favor of the low carbohydrate diets (low to moderate certainty evidence), which persisted at two years but the latter was based on data available from only two of the studies (73,93).

Change from baseline of fasting LDL cholesterol concentration

Twelve studies reported data on this outcome (63,66,68,72-74,78,84,93,94,96,97) with little to no difference demonstrated between the two diet arms at any time point (moderate to high certainty evidence). See **Figure 7**.

Change from baseline of body weight

A total of 16 studies provided data for this outcome (63,66-68,72-75,78,81,83,84,93,94,96,97). See **Supplemental Figure 4**. There was a small effect (MD -2.04 kg, 95% CI: -3.23, -0.85) only at ≥ 8-16 weeks in favor of low carbohydrate food (high certainty evidence).

Change from baseline of BMI

Seven studies evaluated the effect of the two diets on BMI over time (68,72,73,83,93,94,97). There was little to no difference between the two dietary approaches at assessed time points (low to high certainty evidence). See **Supplemental Figure 5**.

Change from baseline of waist circumference

Change of waist circumference was measured in six studies (63,68,72,73,93,96). There was no to little difference between low carbohydrate food and low fat food at assessed time points (low to high certainty evidence). See **Supplemental Figure 6**.

Change from baseline of blood pressure

Seven studies investigated the effects of both types of diets on blood pressure (66,73,84,93,94,96,97). For both systolic as well as diastolic blood pressure, there were possibly no differences in effects between the two diets (low to high certainty evidence), except at six months, where diastolic blood pressure probably declined more on low carbohydrate food (MD -1.91 mmHg, 95% CI: -3.63, -0.18). See **Supplemental Figure 7 and 8**.

Change from baseline of quality of life

Four studies provided data on quality of life (66,73,96,97). The data in the study of Davis et al (66) were reported in a subsequent paper published in 2012 (see Supplemental Table 5), but they were not reported separately per treatment arm, which did not permit reliable conclusions to be drawn regarding the effects of each individual diet on quality of life. The authors reported that the primary goal of their analysis was "to determine whether the dietary strategy used for weight loss would have differential effects on quality of life". Of the 46 out of 105 participants who completed the study, there were reductions in the Diabetes-39 questionnaire scores related to sexual function, energy and mobility but the investigators "did not observe any changes in diabetes-specific quality of life measures that differed between dietary arms". Data of Wolever et al (96) were also addressed in a subsequent paper (see Supplemental Table 5). A Quality of Life questionnaire was used which was adapted from validated questionnaires. No exact data were provided but the authors reported “no significant differences between baseline and end of study and no significant changes among diets”.

Effects of dietary interventions per time window

Short term measurements (up to 8 weeks)

The data up to eight weeks as well as the certainty of evidence are summarized in **Table 3**.

However, as the possible causes of heterogeneity are not fully captured in this table, we provide details to accompany this table and the following tables.

The substantial heterogeneity between studies for HbA1c is likely due to a significant increase in HbA1c levels in the high carbohydrate (low fat) group in the study of Lerman-Garber et al (78), which may be attributable to the baseline imbalance of HbA1c and/or by the relatively high (60%) carbohydrate content of the high carbohydrate diet. Furthermore, consideration should also be given to the rather large (35%) drop-out rate in this study.

For fasting glucose, heterogeneity was almost completely caused by the study of Hockaday et al, in which the low fat diet group did clearly better than the low carb group (75). However, this may have been due to the fact that plasma glucose levels at baseline were substantially higher in the participants receiving the low fat diet.

Heterogeneity between studies for fasting triglycerides was primarily caused by Gumbiner et al, which reported a considerable reduction of plasma triglyceride concentrations in participants on the low carbohydrate diet (74). This may have been due to the significant difference in macronutrient composition between the dietary interventions in this study. The low carbohydrate diet had only 9.5 en% of carbohydrate and 70 en% of fat, while the low fat diet had 70 en% of carbohydrates and only 10% of fat. All of the other included studies had approximately 40 en% of carbohydrates in their low carb intervention.

The heterogeneity between studies for fasting HDL-cholesterol was largely attributable to the results reported by Miyashita et al (81). It remains unclear why the HDL-cholesterol levels increased more in response to low carb food in this study (even in the absence of effects on triglyceride concentrations) as compared to other included studies.

<u>Medium term measurements (≥ 8-16 weeks)</u>

The results for this time window for each of the prespecified outcomes as well as the certainty of the evidence are presented in **Table 4**.

Heterogeneity for the pooled data of HbA1c is primarily caused by the study of Nielsen et al (83). There was a larger reduction in HbA1c levels in this study than in the other three studies, probably because the carbohydrate content of the low carbohydrate diet in this study was only 20 en%, as opposed to 30-40% in the other three studies. Moreover, this CCT was at serious risk of bias, as participants who were assigned to low carbohydrate food were recruited via an information meeting on alternative dietary interventions, whereas the control group did not attend that meeting for unclear reasons (but likely because they were not interested). Thus, the intervention group displayed interest in their condition and in alternative dietary strategies, whereas participants in the control group were apparently less than interested. Affinity with or preference for a specific intervention is most likely to have an impact on the outcome.

Regarding change from baseline in BMI, two studies both compared low carb versus low fat diet, but they were very different in other respects. The CCT (83) as just mentioned has a serious risk of bias (see above), and the dietary interventions studied were calorie restricted and very low carb (20 en%), and participants were instructed to exercise 30 min a day. Conversely, in the study of Walker et al (94) the low carbohydrate intervention had 40 en% carbohydrate, it was not calorie restricted and the participants were advised to maintain usual physical activity. These differences may, to a large extent, explain the heterogeneity between the studies.

The heterogeneity in the data of change in systolic blood pressure (greater decline on low carbohydrate food in Davis et al (66)) may have been caused by the fact that the en% of carbohydrates of actual intake in the low carb group at that time point was 24% in the study of Davis et al (66) compared to 40 en% in Walker et al (94).

<u>Medium term measurement (≥ 16-26 weeks)</u>

Data of the prespecified outcomes as well as the certainty of evidence for this time period can be found in **Table 5**.

Heterogeneity between studies for HbA1c was caused by two of the studies (67,93). The reductions of HbA1c in both of these were substantial in both diet arms, but it remains unclear why the difference in HbA1c reduction between low carb- and low fat diets in these studies is relatively small. The participant characteristics, medications used (and discontinuance of medication during the study), dietary composition or dropout rate do not appear to differ significantly between studies. Tay et al reported a statistically significant difference in favor of the low carbohydrate intervention between the two diet groups in participants with a high HbA1c at baseline (>7.8%), but there was no difference between both groups as a whole (93). Heterogeneity between studies for fasting glucose was primarily caused by the same two studies (67,93). It remains unclear why these studies differ from the other studies in terms of the response of fasting plasma glucose concentrations to dietary intervention.

The heterogeneity between studies for fasting HDL-cholesterol is fully attributable to the slight reduction of HDL-cholesterol in response to low carb food in two of the studies (67,72). This discordance in the data may be due to the relatively high baseline HDL-cholesterol levels in both studies, which paves the way for random changes (regression) towards a lower mean on subsequent measurement. We were unable to identify other differences between the included studies which might provide an explanation for the heterogeneity/ variability in HDL-cholesterol levels in response to the dietary intervention.

For the outcome change from baseline in body weight as well as BMI, heterogeneity was essentially caused by two of the studies (72,83), showing the greatest differences in body weight favoring the low carbohydrate group. The CCT by Nielsen et al (83), was at serious risk of bias, as discussed under the former time window with the people in the low carbohydrate diet group being presumably more adherent due to the counselling ahead of the study. Although the energy content of the actual dietary intake was not reported, the very low carbohydrate diet utilized in the study by Goday et al (72) had far less calories (600-800 kcal

in the "active" phase) than the low fat diet ("500-1000 kcal *restriction* according to each individuals basal metabolic rate").

All of the heterogeneity between the studies evaluating change from baseline in waist circumference can be attributed to Goday et al (72), perhaps because the low carbohydrate ketogenic diet in this study had far fewer calories than the low fat intervention, whereas both interventions were energy-matched in the other studies (73,93).

Both Guldbrand et al and Yamada et al reported six month data on changes in quality of life, but used different measurement scales (73,97). Quality of life data from the study of Guldbrand et al (73) were published in a subsequent paper in 2014 (see Supplemental Table 5). Data was collected using the generic Short Form-36 (SF-36), a 36 item questionnaire covering eight health domains with each domain scoring from 0 to 100 (higher score indicating better quality of life). The investigators calculated both the combined physical component score (PCS) and the Mental Component Score (MCS). The questionnaire was completed at month six by 23 patients in the low carbohydrate group and by 22 in the low fat intervention group. The change from baseline in PCS at six months was -0.90 (SD 7.44) in the low carbohydrate group versus 0.50 (6.30) in the low fat group. The change from baseline in MCS was -1.70 (SD 8.43) in the low carbohydrate diet group compared to 1.80 (6.30) in the low fat group.

In the study of Yamada et al (97), two different instruments were used; the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Problem Areas in Diabetes scale (PAID). The DTSQ measures treatment satisfaction in diabetes patients and covers six satisfaction items on a seven point Likert scale from 0 to 6, with a maximum of a total of 36 points with higher scores indicating greater satisfaction (98). The PAID score covers a 20-item survey, and evaluates the degree to which diabetes management and/or feelings about diabetes are problematic to people with diabetes (99). Each item is scored on a Likert scale

ranging from 0 to 4 with the sum of all item scores multiplied by 1.25 to obtain the overall PAID score (range from 0 to 100), with a higher score reflecting more significant diabetes-related emotional distress. For the DTSQ the total score increased from 24.0 (SD 6.6) by 3.60 (SD 3.98) at 6 months in the 12 patients on a low carbohydrate diet compared to an increase from 21.6 (SD 3.3) by 3.10 (2.72) in the 12 patients on the calorie restricted (low fat) diet Both diets showed small improvements in quality of life with no to little difference between the diets. The PAID scores changed from 42.1 (SD 13.5) by -4.30 (8.12) in the low carbohydrate diet group and from 57.8 (SD 12.6) by -0.60 (7.78) in the calorie restricted (low fat) diet group. Although the magnitude of changes in both quality of life instruments required for clinical significance (minimal important difference) has not been established, the subtle improvements measured in both intervention arms are unlikely to be of clinical relevance.

Long term measurement (> 26 weeks)

The long-term measurement results of the prespecified outcomes and the certainty of evidence are summarized in **Table 6**.

The substantial heterogeneity between studies of change from baseline of fasting glucose is almost fully attributable to the differing results of two of the studies (75,96). The beneficial effect of low fat food in the study by Hockaday et al may have been biased by the higher glucose concentration levels at baseline in the participants assigned to low fat food (75). The relatively minor difference in fasting glucose concentrations in response to low fat *versus* low carbohydrate food in the study by Wolever et al (96), may have been due to the fact that the low fat intervention contained only low glycemic index carbohydrates within the carbohydrate component. In fact, in this study the effects of low fat, low glycemic index food were compared with those of low carbohydrate food.

The heterogeneity between the studies for change from baseline of fasting triglycerides is fully attributable to the more substantial decrease in triglycerides in response to carbohydrate

restriction in one (68) of the studies. A possible explanation could be that baseline plasma triglycerides concentrations were substantially higher in this study than in any of the other included studies (elevated levels almost always predict better response).

The heterogeneity between the studies for pooled data on fasting HDL-cholesterol is fully explained by the relatively robust increase of HDL-cholesterol concentrations in response to low carb food in the study by Elhayany et al, which is most likely explained by the considerable concomitant decline of plasma triglyceride concentrations achieved in that study (68). Reduction of circulating (VLDL) triglycerides limits the exchange of cholesteryl esters between HDL and VLDL particles and thereby increases HDL-cholesterol.

Almost all heterogeneity between the studies of the meta-analysis for data on change from baseline of LDL-cholesterol was caused by the data from one study (68), which reported diametrically opposing results (larger decline of LDL cholesterol in response to the low carb diet). This difference is difficult to explain, but may be due to the differences in gender distribution and ethnicity between participants. It may also reflect differences in diet quality between the studies. Elhayany et al (68) compared low carb, low glycemic index Mediterranean food with low fat food according to ADA guideline, including mixed high- and low glycemic index carbohydrates. The quality (i.e. type of distinct macronutrients) of the dietary interventions in the study by Davis et al (66) remains obscure, but may have differed substantially.

The only study addressing quality of life at one and two years was Guldbrand et al (73). At 12 months, the change from baseline in the low carbohydrate group (n = 27) for PCS was 2.60 (SD 6.50) and 0.60 (SD 6.32) in the low fat group (n = 28) and for MCS 0.90 (SD 4.34) versus 1.10 (SD 6.11). At two years the change from baseline in PCS for the low carbohydrate group (n = 25) was -2.70 (SD 8.49) compared to -1.70 (6.64) in the low fat group (n = 29) with a mean difference of -1.00 (95% CI: -5.11, 3.11; P = 0.63). For MCS the changes from

baseline were 1.40 (SD 4.59) in the low carbohydrate diet group and 0.30 (6.08) in the low fat group with a mean difference of 1.10 (95% CI: -1.75, 3.95; P = 0.45).

DISCUSSION

Principal findings and interpretation

This systematic review of 36 randomized controlled intervention studies and controlled clinical trials (including 2161 patients) is the first to comprehensively and specifically compare the effects of low carbohydrate *versus* low fat food on glucose control, the plasma lipid cardiovascular risk profile and bodyweight of people with DM2. Our results suggest that there is, in general, little to no difference between the metabolic effects of diets containing up to 40 en% carbohydrates ("low carb") and diets containing up to 30 en% fat ("low fat"). A low carb diet may reduce HbA1c compared to a low fat diet, particularly in the short- and medium term up to one year, but we are uncertain about this effect. At two years, the difference between the effects of either diet on HbA1c had disappeared. The fact that all metabolic measurements tend to return to baseline values in *both* groups after two years, suggests that lack of compliance with dietary prescriptions may have played a role here. Although carbohydrate restriction more clearly improves other metabolic parameters at many of the pre-specified time points, the differences with the effects of low fat food are of doubtful clinical importance and supported by only low to moderately certain evidence. Since the minimal clinically important difference for most of these metabolic parameters has not been determined, our inference regarding clinical meaning is arguable.

Both dietary strategies similarly affect LDL cholesterol concentrations, which may come as a surprise, as (some) saturated fatty acids tend to increase LDL cholesterol levels. However, this is particularly true if dietary polyunsaturated fatty acids are substituted by saturated ones. Substitution of carbohydrates by saturated fat has less of an effect on LDL cholesterol levels

(100). Blood pressure response (systolic as well as diastolic) was not significantly different either, although low carb food may reduce diastolic pressure slightly more than low fat food in the medium term. All of these metabolic effects occur in the face of little to no differences in losses of bodyweight or waist circumference. There may be no important improvement of quality of life in response to either dietary strategy in the few studies assessing this outcome. The certainty of evidence for the secondary outcomes varies from very low to high, but is predominantly low at the various time points.

Although all measurable differences between the metabolic effects of low carb diets versus those of low fat diets were in favor of low carb food, they were small, of uncertain clinical importance and supported by only low to moderate certainty evidence according to GRADE. These observations are counterintuitive, since carbohydrates are the only (direct) source of glucose in our diet, and restriction of carbohydrate consumption is therefore expected to lower blood glucose and HbA1c as well as triglyceride concentrations. Substantial clinical and methodological heterogeneity among eligible studies may contribute to the apparent lack of differences (see below). The relatively mild restriction of carbohydrate content of most low carbohydrate diet interventions included in the review (25-40 en%) may have also played a role. However, the results of three studies comparing very low carb ketogenic diets with low fat interventions (72,74,93) do not substantially deviate from those of other included trials.

Strengths and limitations of the review

The key strengths of our review are underlined by the more prescriptive approach used in setting out our selection criteria, which have enabled the answering of a clearly defined clinical question on the comparison of two explicit dietary strategies for management of DM2. Any methodological difference between this review and earlier reviews is most likely

reflected in the rapidly evolving nature of the process of conducting systematic reviews, such as the use of the GRADE approach to evaluate the certainty of evidence.

The high degree of clinical and methodological heterogeneity between the included studies may be the most important reason for the apparent lack of relevant distinction between the effects of both dietary strategies. For example, the energy percentage of macronutrients in the prescription diets differed considerably. Some low carb interventions were indeed very low (< 20 en%) in carbohydrate (72,74,93), while others were only mildly restrictive, and previous reports suggest that HbA1c declines in proportion to the energy percentage of carbs in the diet (10). Similarly, in some studies (74,81) the fat content of the low fat intervention was much lower (< 15en%) than in others. Moreover, the nature of the fat component of low carb diets differed considerably among studies, which is a potential confounder of study outcomes, as distinct fatty acids differentially impact (glucose) metabolism (101). Also, the quality of the carbohydrate component (simple or complex) of interventions often remains obscure, while it is of critical importance for the metabolic response to dietary regimes (102). Numerous other aspects differed considerably among studies, including calorie content, exercise prescription, provision of food by the study center and reporting actual food intake. Medication regimes (glucose-, blood pressure-, and/or lipid lowering) were modified in some studies, whereas they remained unchanged in others. Some of the studies included medication naïve patients, while other reports failed to document medication details adequately. Notably, and significantly, in all of the studies which included patients on medication *and* adequately reported eventual adaptations (66,73,83,93), except one (67), glucose-lowering drug doses were reduced in participants on low carb food, but not in those on low fat food. Unfortunately, inconsistent methods of quantification and reporting precluded reliable statistical analysis of changes in drug doses.

Comparison to other (systematic) reviews

We identified 21 systematic reviews and evidence syntheses focusing on the effects of low carbohydrate diets on metabolic outcome parameters, dating back to 2006 (for a complete list see **Supplemental Table 7**). Only one of these specifically compared the effects of low carbohydrate- to those of low fat diets on components of the metabolic syndrome in the treatment of DM2 (103). The low carb dietary interventions in the studies included in the review contained < 40 en% carbohydrate, and the low fat diets had < 25 en% fat. The investigators concluded that "replacing fat with carbohydrate could deteriorate insulin resistance", with adverse effects on triglycerides and HDL cholesterol (which could be avoided by energy restriction). There were no significant differences between the effects of either diet on HbA1c or blood glucose concentration in fasting condition. However, the studies included in the review lasted for a maximum of 12 weeks, with the vast majority lasting only two to six weeks, which is far too short a period to reliably judge the effects on HbA1c. The other available reviews of low carbohydrate interventions had either different outcome parameters (primarily weight loss), or included studies with other comparison diets, or focused on other target groups (i.e. obese individuals).

Implications of the findings

This analysis does not support the long-held preference for low fat diets as the default dietary intervention for DM2. Instead, the results suggest that, if it fits the patients' preferences, restriction of carbohydrate may be slightly better, although the clinical benefits are uncertain.

Unanswered questions and future research

Randomized controlled intervention studies comparing the effects of very low carbohydrate (ketogenic) diets *versus* those of low fat diets in people with DM2, wherein drug dosing is one of the primary study outcomes, are urgently needed. Moreover, the clinical importance of

personalized dietary interventions is a major issue that requires evaluation in future studies. It is highly unlikely that a “one size” solution fits all patients equally well. Indeed, it has been shown that healthy people eating identical meals present highly variable post-meal glucose responses (104). This is probably also true in people with DM2. Some studies (105) suggest that the primary site of insulin resistance (liver, muscle, adipose or combinations thereof) dictates the optimal diet composition for individuals with DM2. Finally, since it appears that the key challenge with dietary interventions is in ensuring their long-term adherence, future studies should focus more on methods to sustain necessary adaptations. This will require a comprehensive systems approach, in which personal preferences, personality traits, socio-economic status and family circumstances in addition to personal aspects of physiology should be taken into account (106,107).

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Table 1 Summary of characteristics of included studies and risk of bias (see also Supplemental Table 6 for all details and extensive version)

Study	Methods	Participants	Interventions	Outcomes	Risk of bias
Blades 1995 (62) Not included in results see Supplemental Table 4	RCT cross-over Dallas, Texas, US	10 (all men) Mean age 61.3 years DM2 BMI: 28.6 kg/m^2	6 weeks (cross-over) A: High-monounsaturated-fat (low carbohydrate) diet (high- MUFA diet) B: High-carbohydrate diet (low fat) diet 9 days washout in between Food prepared in metabolic kitchen, taken home Energy intake adjusted to keep constant body weight A: High-MUFA diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat B: High-carbohydrate (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat No change in physical activity Medication: all patients were taking 17.8 ± 13 mg glipizide/day	Oral-fat tolerance test Triacylglycerol and retinyl palmitate concentration Post-heparin lipase test Fasting plasma total cholesterol, VLDL, HDL and LDL	High risk (washout too short)
Bozzetto 2012 (63)	RCT Naples, Italy	45 (37 men/8 women) Mean age 57-63 years DM2 BMI: 28-31 kg/m^2	8 weeks (we used arm A and B) A: High-MUFA (low carbohydrate) diet (MUFA group) for 8 weeks (n = 8) B: High-carbohydrate, high-fiber, low-glycemic index (low fat) diet (CHO/fiber group) for 8 weeks (n = 9) C: High-MUFA (low carbohydrate) diet plus physical training (MUFA+Ex group) for 8 weeks (n = 9) D High-carbohydrate, high-fiber, low-glycemic	Liver fat content (^{1}H NMR) spectroscopy examination) HbA1c Fasting plasma glucose Fasting plasma triglyceride Fasting plasma cholesterol Fasting lipoprotein	High risk (attrition 20%)

			index (low fat) diet plus physical training (CHO/fiber+Ex group) for 8 weeks (n = 10) Frequent follow-up and support by dietitian Isoenergetic diets to keep body weight constant A: High-MUFA (low carbohydrate) diet: 40 en% carbohydrates, 18 en% protein, 42 en% fat (fiber 10 g/1000 kcal) B: High-carbohydrate (low fat) diet: 52 en% carbohydrates, 18 en% protein, 30 en% fat (fiber 28 g/1000 kcal) 26/45 used metformin in addition to diet	fractions Anthropometrics (body weight, height, and waist circumference) Cardiorespiratory fitness Adherence to the dietary treatments	
Chen 1995 (64) Not included in results see Supplemental Table 4	RCT cross-over Palo Alto, California, US	9 (6 men/3 women) Mean age 49 years DM2 BMI: 27.5 kg/m^2	6 weeks (cross-over) A: Low carbohydrate diet B: Low fat diet No washout between diets All food consumed during the study period was provided by the General Clinical Research Center kitchen. Total daily caloric intake was calculated for each subject to achieve weight maintenance during the 6-week dietary periods. Diets were isocaloric Low carbohydrate diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat Low fat diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat No medication (other than a sulphonylurea compound)	Fasting plasma glucose/fasting plasma insulin Fasting plasma triglycerides Retinyl ester concentrations Very-low-density lipoprotein-TG turnover Lipoprotein lipase measurement	High risk (no washout)

Coulston 1989 (65) Not included in results see Supplemental Table 4	RCT cross-over Palo Alto, California, US	8 (5 men/3 women) Mean age 66 years DM2 BMI: 25.5 kg/m^2	6 weeks (cross-over) A: Low carbohydrate diet B: Low fat diet No washout between diets All food consumed during the study period was provided by the General Clinical Research Center kitchen. Total daily caloric intake was calculated for each subject to achieve weight maintenance during the 6-week dietary periods. Low carbohydrate diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat Low fat diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat No medication (other than a sulphonylurea compound)	Fasting plasma glucose/fasting plasma insulin Fasting plasma triglycerides Fasting cholesterol Fasting and postprandial plasma samples on days 41 and 42 of each diet period at hourly intervals for determining glucose and insulin concentrations Fasting VLDL, LDL, HDL at day 41 and 42 of each diet 24 h urine collection on day 41 for glucose excretion	High risk (no washout)
Davis 2009 (66)	RCT Bronx, New York, US	105 (23 men/82 women) Mean age 55 years DM2 BMI: 35-37 kg/m^2	One year A: Low carbohydrate diet (n = 55) B: Low fat diet (n = 50) Frequent follow-up and support by dietitian Calorie restricted aiming at weight loss 1 pound a week A: Low carbohydrate diet: 24 en% carbohydrates, 27 en% protein, 49 en% fat B: Low fat diet: 53 en% carbohydrates, 22 en% protein, 25 en% fat Recommendations to achieve 150 min of physical activity each week	Weight Glycemic control (HbA1c) Blood pressure Fasting total cholesterol, HDL, LDL, triglycerides	Unclear risk (performance bias)

			Medication: at randomization, the algorithm included reducing insulin dosages by 50% and discontinuing sulphonylurea in the low-carbohydrate arm and reducing insulin by 25% and decreasing the sulphonylurea dose by 50% in the low-fat arm		
De Bont 1981 (67)	RCT Multicenter, UK	148 (all women) Mean age 55 years DM2 Weight: 72-73 kg	6 months A: Low carbohydrate diet (n = 65) B: Low fat diet (n = 71) Regular follow-up and support by dietitian A: Low carbohydrate diet: carbohydrates < 40 en% B: Low fat diet: fat < 30 en% Medication: oral hypoglycemic drugs: low carb diet group 2%, low fat diet group 1%	Weight and height Blood pressure every month Fasting blood glucose and HbA1c Fasting cholesterol, HDL-cholesterol, and triglycerides	Unclear risk (selection bias, performance bias)
Elhayany 2010 (68)	RCT Multicenter, Israel	259 (93 men/86 women and 80 gender unknown) Mean age 55 years DM2 BMI: 31-31.8 kg/m^2	One year A: Low carbohydrate Mediterranean diet (n = 61) B: Low fat diet (n = 55) C: Traditional Mediterranean diet (n = 63) Frequent follow-up and support of a dietitian Diets were isocaloric and calorie restricted A: Low carbohydrate Mediterranean diet: 35 en% carbohydrates, 20 en% protein, 45 en% fat B: Low fat diet (ADA): 50 en% carbohydrates, 20 en% protein, 30 en% fat C: Traditional Mediterranean diet: 50 en% carbohydrates, 20 en% protein, 30 en% fat 30–45 min of aerobic activity at least 3 days a	Weight, height, waist and hip circumference Blood pressure every month Fasting blood glucose, plasma insulin, and HbA1c Fasting cholesterol, HDL-cholesterol, and triglycerides Liver enzymes, serum creatinine and urea	High risk (quasi-randomized and 30.9% attrition)

			week Medication: no details of medication during the study but no insulin		
Garg 1988 (69) Not included in results see Supplemental Table 4	RCT cross-over Dallas, Texas, US	10 (all men) Mean age 56 years DM2 BMI: 29 kg/m^2	4 weeks (cross-over) A: High-monounsaturated-fat (low carbohydrate) diet (high- MUFA diet) B: High-carbohydrate diet (low fat) diet 1-3 week washout in between diets Patients hospitalized. Food prepared in metabolic kitchen Diets were isocaloric A: High-MUFA diet: 35 en% carbohydrates, 15 en% protein, 50 en% fat B: High-carbohydrate (low fat) diet: 60 en% carbohydrates, 15 en% protein, 25 en% fat Constant level of physical activity restricted to walking Medication: all patients received a combination of neutral protamine Hagedorn and regular human insulin	Fasting plasma glucose HbA1c Total cholesterol, triglycerides, VLDL, HDL, LDL Free insulin 24 h urine	High risk (washout too short)
Garg 1992 (70) Not included in results Supplemental Table 4	CCT cross-over Dallas, Texas, US	10 (all men) Mean age 61.5 years DM2 BMI: 27.7 kg/m^2	4 weeks (cross-over) A: High-monounsaturated-fat (low carbohydrate) diet (high- MUFA diet) as a liquid formula B: High-carbohydrate (low fat) diet as a liquid formula No washout between diets Patients hospitalized. Energy intake was adjusted to maintain a constant	Fasting plasma glucose, plasma insulin Fasting glucagon, and C-peptide Fasting triglycerides, VLDL, HDL, LDL GHb concentration 24-h urine for glucose determination	Serious risk (no washout)

			body weight A: High-MUFA diet (liquid formula): 38 en% carbohydrates, 17 en% protein, 45 en% fat B: High-carbohydrate (low fat) diet (liquid formula): 65 en% carbohydrates, 15 en% protein, 20 en% fat Constant level of physical activity restricted to walking Medication: oral hypoglycemic drugs if any were discontinued		
Garg 1994 (71) Not included in results see Supplemental Table 4	RCT cross-over Multicenter, US	42 (33 men/9 women) Mean age 58 years DM2 BMI: 28.1 kg/m^2	6 weeks (cross-over) A: High-monounsaturated-fat (low carbohydrate) diet (high-MUFA diet) B: High-carbohydrate (low fat) diet 1 week washout in between diets Food prepared at all centers Diets were isocaloric A: High-MUFA diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat B: High-carbohydrate (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Constant level of physical activity Medication: all patients were taking around 17 mg glipizide/day	Fasting plasma glucose, plasma insulin HbA1c Total cholesterol, triglycerides, VLDL, HDL, LDL	High risk (washout too short)
Goday 2016 (72)	RCT Multicenter, Spain	89 (31 men/58 women) Mean age 55 years DM2	4 months A: Very low calorie-ketogenic diet (n = 45) B: Low calorie (low fat) diet (n = 44) Frequent follow-up and support by dietitian	Fasting plasma glucose HbA1c, HOMA-IR Fasting plasma triglycerides, total	Unclear risk (selection bias, performance

		BMI: 33.3 kg/m^2	Calorie restricted A: Very low calorie-ketogenic diet: carbohydrates < 50 g B: Low calorie (low fat) diet: 45-60 en% carbohydrates, 10-20 en% protein, < 30 en% fat Recommendations to exercise and behavioral modifications Medication: oral antidiabetic medication was continued or diminished/stopped	cholesterol, LDL cholesterol Renal function, liver function, plasma uric acid, sodium and potassium Body weight, BMI, waist circumference Dietary adherence and satisfaction	bias, attrition bias)
Guldbrand 2012 (73)	RCT Multicenter, Sweden	61 (27 men/34 women) Mean age 61 years DM2 BMI: 31.6-33.8 kg/m^2	2 years A: Low carbohydrate diet (n = 30) B: Low fat diet (n = 31) Frequent follow-up and support by dietitian Diets were isocaloric and calorie restricted Low carbohydrate diet: 20 en% carbohydrates, 30 en% protein, 50 en% fat Low fat diet: 55-60 en% carbohydrates, 10-15 en% protein, 30 en% fat Medication: oral antidiabetic medication, or insulin, hypolipidemic and antihypertensive medication when necessary	Body weight, BMI, waist circumference, sagittal abdominal diameters HbA1c, total cholesterol, LDL, HDL, triglycerides Blood pressure Quality of life	Unclear risk (performance and detection bias)
Gumbiner 1998 (74)	CCT Rochester, New York, US	17 (8 men/9 women) Mean age 53 years Obese DM2 BMI: 36.3-37.2 kg/m^2	6 weeks A: High-monounsaturated-fat (low carbohydrate) diet as liquid formula (high-MUFA diet)(n = 8) B: High-carbohydrate (low fat) diet as a liquid formula (n = 9) Frequent follow-up and support in the Clinical	Fasting plasma glucose C-peptide, glucagon Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoproteins A and B	Moderate risk (confounding and performance bias)

			Research Center Calorie restricted A: High-MUFA diet: 10 en% carbohydrates, 20 en% protein, 70 en% fat B: High-carbohydrate (low fat) diet: 70 en% carbohydrates, 20 en% protein, 10 en% fat Constant level of physical activity Medication: oral sulphonylurea agents, insulin, antihypertensive, and lipid-lowering therapies, were discontinued 2 weeks before metabolic testing. Insulin continued	Weight	
Hockaday 1978 (75)	RCT, Oxford, UK	93 (52 men/41 women) Mean age: 51.5 years Weight: 76.4-82.2 kg	1 year A: Low carbohydrate diet (n = 54) B: Modified fat high carbohydrate diet (n = 39) Regular follow-up and support by dietitian Diets were calorie restricted Low carbohydrate diet: 20 en% carbohydrates, 20 en% protein, 40 en% fat Modified fat high carbohydrate diet: 54 en% carbohydrates, 20 en% protein, 26 en% fat No medication	Fasting plasma glucose and insulin Fasting plasma cholesterol Fasting triglycerides Weight	Unclear risk (selection bias, performance bias, baseline imbalance)
Iqbal 2010 (76) Not included in results see Supplemental Table 4	RCT Multicenter, US	144 (129 men/15 women) Mean age 60 years DM2 BMI: 36.9-38.1 kg/m^2	2 years A: Low carbohydrate diet (n = 70) B: Low fat diet (n = 74) Regular follow-up and support by dietitian Low carbohydrate diet: 30 g/day and deficit of 500 kcal/day Low fat diet: < 30% en% fat	Weight Plasma glucose and HbA1c Fasting plasma cholesterol Fasting triglycerides, LDL, HDL Blood pressure	High risk (attrition bias 52.3%)

			Regular exercise 30 min 5 days of the week recommended Medication: in low carb group sulfonylurea (57%), metformin (61.4%) thiazolidinediones (8.6%); in low fat group sulfonylurea (43.2%), metformin (52.7%) thiazolidinediones (10.8%)		
Jones 1986 (77) Not included in results see Supplemental Table 4	RCT cross-over Oxford, UK	10 (4 men/6 women) Mean age 64.5 years DM2 Blood glucose > 12 mmol/l	6 weeks (cross-over) A: Low carbohydrate diet B: High carbohydrate (low fat) high fiber diet No washout between diets A: Low carbohydrate diet: 35 en% carbohydrates, 17 en% protein, 48 en% fat B: High carbohydrate (low fat) high fiber diet: 55 en% carbohydrates, 27 en% protein, 18 en% fat Medication: 7 chlorpropamide + metformin, 3 only chlorpropamide	Fasting plasma glucose en insulin HbA1c Total cholesterol, cholesterol in the lipoprotein fractions Triglycerides Platelet phospholipid fatty acid measurements	High risk (no washout)
Lerman-Garber 1995 (78)	RCT, cross-over Mexico City, Mexico	20 (all women) Mean age 60 years DM2 HbA1c>9.5% Poor glycemic control BMI: 25.2 kg/m^2	6 weeks (cross-over) A: High-monounsaturated-fat (low carbohydrate) diet B: High complex carbohydrate (low fat) diet 6 weeks washout in between diets Regular follow-up and support by dietitian A: High-MUFA (low carbohydrate) diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat B: High complex carbohydrate (low fat) diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat Medication: all had oral agents and/or insulin, 69% had hypertension and used diuretics, ACE	Fasting plasma glucose and HbA1c Fasting plasma cholesterol Fasting triglycerides, LDL, HDL	High risk (attrition bias 35%)

			inhibitors, calcium channel inhibitors		
Lopez-Espinoza 1984 (79) Not included in results see Supplemental Table 4	RCT Oxford, UK	59 (34 men/25 women) Mean age 56 years DM2 BMI: 28.7-31.9 kg/m^2	7 years A: Low carbohydrate diet (n = 25) B: Modified fat diet (n = 34) A: Low carbohydrate diet: 40 en% carbohydrates B: Modified fat diet: 30 en% fat	Phospholipid fatty acid composition of platelets Development of retinopathy	Unclear risk (selection bias, performance bias, baseline imbalance)
Lousley 1983 (80) Not included in results see Supplemental Table 4	RCT, cross-over Oxford, UK	15 (gender not reported) Age 51-75 years DM2 High doses oral antiglycemic agents	6 weeks (cross-over) A: Low carbohydrate diet B: High carbohydrate (low fat) high fiber diet No washout between diets A: Low carbohydrate diet: 35 en% carbohydrates, 22 en% protein, 43 en% fat B: High carbohydrate (low fat) high fiber diet: 60 en% carbohydrates, 24 en% protein, 16 en% fat Medication: all continued oral antiglycemic medication	Fasting plasma glucose and insulin Fasting plasma cholesterol, LDL, HDL, VLDL Fasting triglycerides	High risk (attrition bias 26.6%)
Miyashita 2004 (81)	RCT Sakura City, Chiba, Japan	22 (16 men/6 women) Mean age 52.4 years DM2 BMI: 27 kg/m^2	4 weeks A: Low carbohydrate diet (n = 11) B: High carbohydrate (low fat) diet (n = 11) Patients hospitalized Diets were isocaloric and calorie restricted A: Low carbohydrate diet: 40 en% carbohydrates, 25 en% protein, 35 en% fat B: High carbohydrate (low fat) diet: 65 en% carbohydrates, 25 en% protein, 10 en% fat	Fasting plasma glucose Fasting plasma cholesterol, HDL, triglycerides Weight, body fat Measurement visceral and subcutaneous fat mass	Unclear risk (selection bias, performance bias)

			Exercise twice daily recommended (walking) No medication		
Ney 1982 (82) Not included in results see Supplemental Table 4	RCT San Diego, California, US	20 (all women) Mean age 26.6-32 years DM1 and DM2 Pregnant	14-18 weeks A: Control (low carbohydrate) diet (n = 10) B: High carbohydrate (low fat) diet (n = 10) Intensive dietary instructions A: Control (low carbohydrate) diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat B: High carbohydrate (low fat) diet: 65 en% carbohydrates, 20 en% protein, 15 en% fat	Fasting plasma glucose HbA1c Mean amplitude of glycemic excursions Mean 24-h urine loss of glucose Insulin requirement (exogenous)	Unclear risk (selection bias, performance bias)
Nielsen 2005 (83)	CCT Karlshamn, Sweden	31 (gender unclear) Mean age 57.1 years Obese DM2 BMI: 34.2-36.1 kg/m^2	6 months A: Low carbohydrate diet (n = 16) B: High carbohydrate (low fat) diet (n = 15) Diets were calorie restricted A: Low carbohydrate diet: 20 en% carbohydrates, 30 en% protein, 50 en% fat B: High carbohydrate (low fat) diet: 60 en% carbohydrates, 15 en% protein, 25 en% fat Regular daily exercise recommended Medication: in low carb diet group 11 insulin, 15 metformin, 5 sulfonylurea, in high carb low fat diet group 6 insulin, 10 metformin, 5 sulfonylurea	Fasting plasma glucose HbA1c Body weight BMI	Serious risk (confounding bias)
Nutall 2012 (84)	RCT, cross-over Minnesota, Minneapolis, US	9 (all men) Mean age 61 years DM2 BMI: 31 kg/m^2	5 weeks (cross-over) A: Low Biologically Available Glucose (LoBAG) (low carb) diet B: Control (low fat) diet 5 weeks washout in between diets	Total alpha amino acid nitrogen Individual specific amino acids Cortisol and glucagon	Unclear risk (performance bias)

			Food delivered Isocaloric diets, aiming stable weight A: Low Biologically Available Glucose (LoBAG) (low carb) diet: 30 en% carbohydrates, 30 en% protein, 40 en% fat B: Control (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Medication: oral antidiabetic treatment was discontinued, all other medication was continued	24-hour urinary free cortisol, microalbumin, calcium, creatinine, glucose, pH, potassium, sodium, urea and uric acid Plasma and/or urine creatinine, urea nitrogen, sodium, potassium, glucose, uric acid, total cholesterol, HDL cholesterol, triacylglycerol, pre-albumin and albumin Body composition data (weight, measurement of fat-free mass)	
Rodríguez-Villar 2004 (85) Not included in results see Supplemental Table 4	RCT (cross-over) Barcelona, Spain	26 (13 men/13 women) Mean age 61 years DM2 BMI: 28.3 kg/m^2	6 weeks (cross-over) A: High-monounsaturated-fat (low carbohydrate) diet (high-MUFA diet) B: High-carbohydrate (low fat) diet No washout between diets Regular follow-up and support by dietitian Diets were calorie restricted A: High-MUFA (low carbohydrate) diet (high-MUFA diet): 40 en% carbohydrates, 15 en% protein, 40 en% fat (not 100%!) B: High-carbohydrate (low fat) diet: 50 en% carbohydrates, 15 en% protein, 30 en% fat (not 100%!)	LDL resistance to oxidation from the high-carbohydrate diet Weight BMI Fasting serum glucose/insulin HbA1c Total cholesterol, HDL, LDL, VLDL and triglycerides Apolipoprotein B and AI	High risk (no washout)

			Medication: oral hypoglycemic medication		
Samaha 2003 (86) Not included in results see Supplemental Table 4	RCT Philadelphia, US	132 (109 men/23 women) Mean age 54 years Obese adults BMI: 43-4 kg/m^2	6 months A: Low carbohydrate diet (n = 64) B: Low fat diet (n = 68) Intensive follow-up and support by dietitian A: Low carbohydrate diet: < 30 g/day carbohydrate B: Low fat diet: < 30 en% fat and calorie restricted 500 kcal per day No specific exercise was recommended Medication: many were taking lipid lowering medications, antihypertensive and hypoglycemic agents	Weight Blood pressure Total cholesterol, HDL, LDL, triglycerides Fasting glucose and insulin	High risk (attrition bias 40.1%)
Saslow 2017 (87) Not included in results see Supplemental Table 4	RCT Multicenter, US	25 (10 men/15 women) Mean age 56 years DM2 Weight: 90.9-109.7 kg	32 weeks A: Very low carbohydrate diet (n = 12) B: Control (low fat) diet (n = 13) Intensive follow-up, lifestyle recommendations, and intensive support of dietitian A: Very low carbohydrate diet: < 20 g carbohydrates B: Control (low fat) diet In very low carb diet group people were encouraged participants to increase their level of physical activity Medication: patients were allowed to continue metformin but no other medication	HbA1c Fasting serum HDL cholesterol, LDL cholesterol, triglycerides Weight Psychological self-report (Diabetes Distress Scale) Center for Epidemiological Studies Depression Scale (CESD) Modified Differential Emotions Scale (mDES) Self assessed physical symptoms with adapted Short Form Health survey to measure of health-	High risk (performance bias and attrition bias 28%)

				related quality of life, to assess vitality (energy and fatigue) Dietary Self-Report (My FitnessPal)	
Shah 2005 (88) Not included in results see Supplemental Table 4	RCT, cross-over Multicenter, US	42 (33 men/9 women) Mean age 58 years DM2	6 weeks (cross-over) A: High-cis-monounsaturated-fat (low carbohydrate) diet (high-MUFA diet) B: High-carbohydrate (low fat) diet 1 week washout between diets Food prepared in metabolic kitchen, taken home, aim maintaining body weight A: High-MUFA diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat B: High carbohydrate (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Maintain usual level of activity Medication: Blood pressure medication kept stable, no info on antidiabetic drugs	Blood pressure Heart rate	High risk (washout too short)
Shai 2008 (89)	RCT Dimona, Israel	322 (277 men/45 women) Mean age 52 years BMI ≥ 27 kg/m^2 or DM2	2 years A: Low carbohydrate diet (n = 109) B: Low fat diet (n = 104) C: Mediterranean diet (n = 109) Intensive support and follow-up by dietitian Only the low fat and the Mediterranean diet were calorie restricted A: Low carbohydrate diet: < 20 g and later 120	Weight BMI Waist circumference Cholesterol, LDL, HDL, triglycerides Fasting plasma glucose/insulin Plasma high-sensitivity C-reactive protein Plasma high-molecular-	Unclear risk (selection bias, performance bias, attrition bias 11.5%)

			carbohydrates B: Low fat diet: < 30 en% fat Medication: 6-12% used oral antidiabetics	weight adiponectin Plasma leptin Liver function tests HOMA-IR HbA1c in the diabetic patients (data for n = 36)	
Simpson 1979 (90) Not included in results see Supplemental Table 4	RCT, cross-over Oxford, UK	18 (15 men/3 women) Mean age 54 years DM2	6 weeks (cross-over) A: Low carbohydrate diet B: High carbohydrate (low fat) diet No washout between diets Diets were isoenergetic A: Low carbohydrate diet: 40 en% carbohydrates B: High carbohydrate (low fat) high fiber diet: 60 en% carbohydrates Medication: 14 sulfonylurea	Fasting plasma glucose Triglycerides HbA1c Cholesterol, HDL, LDL, VLDL Weight	High risk (attrition bias 22.2%, no washout)
Simpson 1981 (91) Not included in results see Supplemental Table 4	RCT, cross-over Oxford, UK	18 (10 men/8 women) Mean age 52.5 years DM2	6 weeks (cross-over) A: Low carbohydrate diet B: High carbohydrate (low fat) diet No washout between diets Diets were isoenergetic A: Low carbohydrate diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat B: High carbohydrate (low fat) high fiber diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat Medication: 14 sulfonylurea, 1 also on metformin	Fasting plasma glucose Triglycerides HbA1c Cholesterol, HDL, LDL, VLDL	High risk (no washout)

Simpson 1982 (92) Not included in results see Supplemental Table 4	RCT, cross-over Oxford, UK	10 (8 men/2 women) Mean age 58 years DM2	4 weeks (cross-over) A: Low carbohydrate diet B: High carbohydrate (low fat) diet No washout between diets A: Low carbohydrate diet: 35 en% carbohydrates, 20 en% protein, 45 en% fat B: High carbohydrate (low fat) high fiber diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat Medication: 8 sulfonylurea	Fasting plasma glucose Triglycerides HbA1c Cholesterol, HDL, LDL, VLDL Weight	High risk (no washout)
Tay 2014 (93)	RCT Adelaide, Australia	115 (66 men/49 women) Mean age 58 years Obese DM2	24 weeks A: Very low carbohydrate high unsaturated/low saturated fat diet (n = 58) B: High unrefined carbohydrate, low fat diet (n = 57) Diets were isocaloric and calorie-restricted Intensive support and follow-up by dietitians A: Very low carbohydrate diet: 14 en% carbohydrates, 28 en% protein, 58 en% fat B: High unrefined carbohydrate, low fat diet: 53 en% carbohydrates, 17 en% protein, <30 en% fat Exercise program Medication: 87 used metformin, 12 insulin, 36 sulfonylurea, 6 thiazolidinediones, equally balanced between groups	HbA1c Glycemic variability Antiglycemic medication changes Blood lipids (total cholesterol, LDL, HDL, triglycerides Blood pressure Weight Fasting blood glucose Waist circumference	Unclear risk (performance bias, attrition bias 19.1% and reporting bias) In follow-up paper in 2018 (see Supplemental Table 5) 2 year data are reported
Walker 1995 (94)	RCT, cross-over Geelong, Australia	24 (9 men/15 women) Mean age 58.3 years	3 months (cross-over) A: Modified fat (low carbohydrate) diet B: High carbohydrate (low fat) diet 1 month washout between diets	Fasting plasma glucose/fasting plasma insulin Body weight/BMI	Unclear risk (performance bias, and unclear how

		DM2 BMI: 28.8-29.1 kg/m^2	Diets were isocaloric Regular follow-up by a dietitian A: Modified fat (low carbohydrate) diet: 40 en% carbohydrates, 14 en% protein, 36 en% fat B: High carbohydrate (low fat) diet: 50 en% carbohydrates, 17 en% protein, 23 en% fat Medication: when necessary low dose hypoglycemic agents	Blood pressure HbA1c Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, VLDL cholesterol Free fatty acids Acceptance of the diets	many initially randomized)
Ward 1982 (95) Not included in results see Supplemental Table 4	RCT, cross-over Oxford, UK	7 (gender not reported) Mean age 55 years DM2	6 weeks (cross-over) A: Low carbohydrate diet B: High carbohydrate (low fat) diet No washout between diets Low carbohydrate diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat High carbohydrate (low fat) diet: 60 en% carbohydrates, 22 en% protein, 18 en% fat Medication: 4 oral hypoglycemic	Fasting plasma glucose/insulin Fasting blood for determination of monocyte insulin receptor binding	High risk (no washout)
Wolever 2008 (96)	RCT Multicenter, Canada	162 (74 men, 88 women) Mean age 60 years DM2 BMI: 30.1-31.6 kg/m^2	1 year A: Low carbohydrate high-monounsaturated fat (high MUFA) diet (n = 54) B: High carbohydrate low glycemic index (low fat) diet (n = 56) C: High carbohydrate high glycemic index (low fat) diet (n = 52) Diets were calorie restricted Frequent and intensive support by dietitian Low carbohydrate high-monounsaturated fat diet:	Fasting plasma glucose/fasting plasma insulin HbA1c Serum cholesterol, triacylglycerol, apolipoprotein (apo) A-I, and apo B, HDL cholesterol, LDL cholesterol CRP	Unclear risk (performance bias, attrition bias 19.8%), reporting bias) In follow-up paper in 2017 (see Supplemental

			39.3 en% carbohydrates, 20.6 en% protein, 40.1 en% fat (actual intake) High carbohydrate low glycemic index (low fat) diet: 51.9 en% carbohydrates, 21.6 en% protein, 26.5 en% fat (actual intake) High carbohydrate high glycemic index (low fat) diet: 46.5 en% carbohydrates, 22.7 en% protein, 30.8 en% fat (actual intake)	Weight Waist circumference Systolic and diastolic blood pressure	Table 5) quality of life data are reported
Yamada 2014 (97)	RCT, Kitasato, Japan	24 (12 men/12 women Mean age 63 years DM2 BMI: 24.5-2 kg/m^2	6 months A: Low carbohydrate diet (n = 12) B: Calorie restricted (low fat) diet (n = 12) Frequent support and training by dietitians A: Low carbohydrate diet: < 70-130 g carbohydrates/day B: calorie restricted (low fat) diet: 50-60 en% carbohydrates, < 20 en% protein, < 25 en% fat Medication: not changed unless hypoglycemia occurred	HbA1c Fasting plasma glucose Bodyweight incidence of hypoglycemic episodes Serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides Blood pressure Markers for atherosclerosis Renal function Liver enzymes Quality of life, the patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Problem Areas In Diabetes (PAID) scale Adverse events	Unclear risk (performance bias, detection bias)

CCT Controlled Clinical Trial; RCT randomized controlled trial

Table 2 Risk of bias using ROBINS-I for Controlled Clinical Trials

	Bias due to confounding	**Bias in selection of the participants in the study**	**Bias in measurement of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of reported result**	**Overall bias**
Garg 1992 (70)	Serious risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias
Gumbiner 1998 (74)	Moderate risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias
Nielsen 2005 (83)	Serious risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias

Table 3 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data up to 8 weeks

Patient or population: people with type 2 diabetes. Data up to 8 weeks,
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change from baseline of HbA1c Follow up: range 4 to 5 weeks	The mean change from baseline of HbA1c ranged from -0.4 to 1.7%	The mean change from baseline of HbA1c in the low carb group was 1.38% lower (-2.64, -0.11)	42 (2 RCTs (78,84))	⊕◯◯◯ VERY LOW [1,2,3]	A low carb diet may reduce HbA1c more than a low fat diet, but we are very uncertain A difference of 0.5% of HbA1c is considered to be clinically important
Change from baseline of fasting glucose Follow up: range 4 to 6 weeks	The mean change from baseline of fasting glucose ranged from -0.11 to -5.43 mmol/l	The mean change from baseline of fasting glucose in the low carb group was 0.01 mmol/l lower (-1.75, 1.72)	158 (4 RCTs (74,75,78,81)) [4]	⊕⊕⊕◯ MODERATE [5,6,7]	Low carbohydrate diet probably results in little to no difference in reduction of fasting glucose compared to the low fat diet Both diets had a potentially important impact on glucose levels in fasting condition
Change from baseline of fasting triglycerides Follow up: range 4 to 6 weeks	The mean change from baseline of fasting triglycerides ranged from -0.88 to 0.73 mmol/l	The mean change from baseline of fasting triglycerides in the low carb group was 0.31 mmol/l lower (-0.76, 0.14)	174 (5 RCTs (74,75,78,81,84)) [4]	⊕⊕⊕◯ MODERATE [5,8,9]	Low carbohydrate diet probably results in little to no difference in reduction of fasting triglycerides compared to a low fat diet
Change from baseline of fasting HDL Follow up: range 4 to 6 weeks	The mean change from baseline of fasting HDL ranged from -0.15 to 0.005 mmol/l	The mean change from baseline of fasting HDL in the low carb group was 0.12 mmol/l higher (0, 0.25)	81 (4 RCTs (74,78,81,84)) [4]	⊕⊕◯◯ LOW [5,10,11]	Low carbohydrate diet may result in small increase of fasting HDL compared to a low fat diet
Change from baseline of fasting LDL Follow up: range 5 to 6 weeks	The mean change from baseline of fasting LDL ranged from -0.31 to -0.1 mmol/l	The mean change from baseline of fasting LDL in the low carb group was 0.07 mmol/l lower (-0.41, 0.27)	59 (3 RCTs (74,78,84)) [4]	⊕⊕⊕◯ MODERATE [3,12]	Low carbohydrate diet probably results in little to no difference in reduction of fasting LDL compared to a low fat diet
Change from baseline of body weight Follow up: range 4 to 6 weeks	The mean change from baseline of body weight ranged from -8.3 to -0.2 kg	The mean change from baseline of body weight in the low carb group was 0.81 kg lower (-2.11, 0.49)	174 (5 RCTs (74,75,78,81,84)) [4]	⊕⊕⊕◯ MODERATE [3,5]	Low carbohydrate diet probably results in little to no difference in reduction of weight loss after 8 weeks compared to a low fat diet Both diets have considerable effects on body weight

Table 3 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data up to 8 weeks

Patient or population: people with type 2 diabetes. Data up to 8 weeks,
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change in baseline of BMI - not measured	No study addressed change of BMI up to 8 weeks after starts of the diets		-	-	We are uncertain about the effect of a low carbohydrate diet compared to a low fat diet on BMI
Change from baseline of waist circumference - not measured	No study addressed change of waist circumference up to 8 weeks after starts of the diets		-	-	We are uncertain about the effect of a low carbohydrate diet compared to a low fat diet on waist circumference
Change from baseline of systolic blood pressure Follow up: mean 5 weeks	The mean change from baseline of systolic blood pressure was -6 mmHg	The mean change from baseline of systolic blood pressure in the low carb group was 2 mmHg lower (-15.29, 11.29)	16 (1 RCT (84))	⊕⊕◯◯ LOW [13]	Low carbohydrate diet may result in little to no difference in reduction of systolic blood pressure compared to a low fat diet Systolic blood pressure declines in both diets in a clinically meaningful extent
Change from baseline of diastolic blood pressure Follow up: mean 5 weeks	The mean change from baseline of diastolic blood pressure was -5 mmHg	The mean change from baseline of diastolic blood pressure in the low carb group was 5 mmHg higher (-1.67, 11.67)	16 (1 RCT (84))	⊕⊕◯◯ LOW [13]	Low carbohydrate diet may result in a little increase to no difference in diastolic blood pressure
Change from baseline in quality of life - not measured	No study addressed change of quality of life up to 8 weeks after starts of the diets		-	-	We are uncertain about the effect of a low carbohydrate diet compared to a low fat diet on quality of life

CHO: Carbohydrates; CI: Confidence interval; vs: versus; Method of analysis for all outcomes: random effect (inverse variance)

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level for serious risk of bias. One study had a 35% drop-out rate
2. Downgraded one level for serious inconsistency ($I^2 = 68\%$)
3. Downgraded one level for serious imprecision, low total sample size
4. One CCT

5. We did not downgrade for risk of bias for the study at high risk of bias, as removing the study did not really alter the effect estimate
6. Downgraded one level for serious inconsistency (I^2 = 81%)
7. We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of less than 3 mmol/l are not considered to be important. Therefore, the effect estimate is rather precise
8. Downgraded one level for serious inconsistency (I^2 = 79%)
9. We did not downgrade for imprecision. We considered reductions of less than 1 mmol/l not to be important to patients. Therefore, the effect estimate is rather precise
10. Downgraded one level for serious inconsistency (I^2 = 73%)
11. Downgraded one level for serious imprecision. Low sample size and the lower boundary of the 95% CI includes no effect
12. We did not downgrade for risk of bias of the CCT or the high drop-out rate of another study as removing these had no important effect on the effect estimate
13. Downgraded two levels for very serious imprecision. Very low sample size, wide CI

Table 4 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of ≥ 8-16 weeks

Patient or population: people with type 2 diabetes. Data of ≥ 8-16 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change from baseline of HbA1c Follow up: range 8 to 16 weeks	The mean change from baseline of HbA1c ranged from -0.8 to 0.1 %	The mean change from baseline of HbA1c in low carb group was 0.55 % lower (-0.93, -0.17)	201 (4 RCTs (63,66,83,94)) [1]	⊕⊕◯◯ LOW [2,3,4]	A low carbohydrate diet may reduce HbA1c slightly compared to a low fat diet A difference of 0.5% of HbA1c is considered to be clinically important
Change from baseline of fasting glucose Follow up: range 8 to 16 weeks	The mean change from baseline of fasting glucose ranged from -1.6 to 0.3 mmol/l	The mean change from baseline of fasting glucose in the low carb group was 0.97 mmol/l lower (-1.66, -0.28)	96 (3 RCTs (63,83,94)) [1]	⊕⊕⊕◯ MODERATE [5,6]	Low carbohydrate diet probably results in a small effect that may not be an important reduction in fasting glucose compared to a low fat diet
Change from baseline of fasting triglycerides Follow up: range 8 to 16 weeks	The mean change from baseline of fasting triglycerides ranged from 0.17 to 0.24 mmol/l	The mean change from baseline of fasting triglycerides in the low carb group was 0.31 mmol/l lower (-0.74, 0.11)	65 (2 RCTs (63,94))	⊕⊕⊕◯ MODERATE [6,7]	Low carbohydrate diet probably results in little to no difference in reduction of fasting triglycerides compared to a low fat diet
Change from baseline of fasting HDL Follow up: range 8 to 16 weeks	The mean change from baseline of fasting HDL was 0 mmHg	The mean change from baseline of fasting HDL in the low carb group was 0.04 mmHg higher (-0.03, 0.11)	65 (2 RCTs (63,94))	⊕⊕⊕◯ MODERATE [6,7]	Low carbohydrate diet probably results in little to no difference in reduction of fasting HDL compared to a low fat diet
Change from baseline of fasting LDL Follow up: range 8 to 16 weeks	The mean change from baseline of fasting LDL ranged from 0.02 to 0.23 mmHg	The mean change from baseline of fasting LDL in the low carb group was 0.08 mmHg lower (-0.34, 0.17)	65 (2 RCTs (63,94))	⊕⊕⊕◯ MODERATE [6,7]	Low carbohydrate diet probably results in little to no difference in reduction of fasting LDL compared to a low fat diet
Changes from baseline of body weight Follow up: range 8 to 16 weeks	The mean changes from baseline of body weight ranged from -3.2 to 0 kg	The mean changes from baseline of body weight in the low carb group was 2.04 kg lower (-3.23, 0.85)	201 (4 RCTs (63,66,83,94)) [1]	⊕⊕⊕⊕ HIGH [5,8]	Low carbohydrate diet results in a small effect that may not be an important reduction in body weight compared to a low fat diet
Change from baseline of BMI Follow up: range 8 to 16 weeks	The mean change from baseline of BMI ranged from -0.7 to -0.3 kg/m2	The mean change from baseline of BMI in the low carb group was 1.19 kg/m2 lower (-3.34, 0.96)	79 (2 RCTs (83,94)) [1]	⊕◯◯◯ VERY LOW [9,10,11]	We are uncertain about the effect of a low carbohydrate diet in reducing BMI compared to a low fat diet

Table 4 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of ≥ 8-16 weeks

Patient or population: people with type 2 diabetes. Data of ≥ 8-16 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change from baseline of waist circumference Follow up: mean 8 weeks	The mean change from baseline of waist circumference was 1 cm	The mean change from baseline of waist circumference in the low carb group was 2 cm lower (-6.29, 2.29)	17 (1 RCT (63))	⊕⊕◯◯ LOW [12]	Low carbohydrate diet may result in little to no difference in reduction of waist circumference compared to a low fat diet
Change from baseline of systolic blood pressure Follow up: mean 16 weeks	The mean change from baseline of systolic blood pressure ranged from -1 to -0.98 mmHg	The mean change from baseline of systolic blood pressure in the low carb group was 0.64 mmHg lower (-7.15, 5.78)	153 (2 RCTs (66,94))	⊕⊕◯◯ LOW [13]	Low carbohydrate diet may result in little to no difference in reduction of systolic blood pressure compared to a low fat diet
Change from baseline of diastolic blood pressure Follow up: mean 16 weeks	The mean change from baseline of diastolic blood pressure ranged from -1 to -0.4 mmHg	The mean change from baseline of diastolic blood pressure in the low carb group was 0.82 mmHg lower (-4.06, 2.42)	153 (2 RCTs (66,94))	⊕⊕◯◯ LOW [13]	Low carbohydrate diet may result in little to no difference in reduction of diastolic blood pressure compared to a low fat diet
Change from baseline of quality of life - not measured	No study addressed change of quality of life up from 8 to 16 weeks after start of the diets		-	-	We are uncertain about the effect of a low carbohydrate diet compared to a low fat diet on quality of life

CHO: Carbohydrates; CI: Confidence interval; vs: versus. Method of analysis for all outcomes: random effect (inverse variance)

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. One CCT
2. Downgraded one level for serious risk of bias. One RCT was at high risk of bias, and the CCT was at serious risk of bias
3. We did not downgrade for inconsistency as the CI were overlapping and I^2 just 54%
4. Downgraded one level for imprecision. Upper boundary is not clinically important
5. We did not downgrade for risk of bias for the study at high risk of bias and the CCT at serious risk of bias, as removing these studies did not really alter the effect estimate
6. Downgraded one level for serious imprecision, low total sample size

7. We did not downgrade for risk of bias for the study at high risk of bias as removing the study did not really alter the effect estimate
8. We did not downgrade for imprecision. Although the minimal important difference is not established, we consider a reduction of less than 5% to be not important. Therefore, the effect estimate is rather precise
9. Downgrading one level for serious risk of bias. The CCT was at serious risk of bias
10. Downgraded one level for serious inconsistency (I^2 = 94%)
11. Downgraded one level for serious imprecision. Low sample size and the 95% CI includes both benefit of the low carbohydrate diet and no difference between the diets
12. Downgraded two levels for very serious imprecision. Very low sample size and the 95% CI includes both benefit of the low carbohydrate diet and no difference between the diets
13. Downgraded two levels for very serious imprecision. 95% CI includes both appreciable harm and benefit

Table 5 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of ≥ 16-26 weeks

Patient or population: people with type 2 diabetes. Data of ≥ 16-26 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change from baseline of HbA1c Follow up: range 16 to 26 weeks	The mean change from baseline of HbA1c ranged from -1.1 to 0 %	The mean change from baseline of HbA1c in the low carb group was 0.26 % lower (-0.5, -0.02)	539 (7 RCTs (66,67,72,73,83,93,97)) [1]	⊕⊕⊕◯ MODERATE [2,3]	Low carbohydrate diet probably results in a small effect that may not be an important reduction in HbA1c compared to a low fat diet
Change from baseline of fasting glucose Follow up: range 16 to 26 weeks	The mean change from baseline of fasting glucose ranged from -1.6 to 0.44 mmol/l	The mean change from baseline of fasting glucose in the low carb group was 0.51 mmol/l lower (-0.91, -0.12)	396 (6 RCTs (67,72,83,89,93,97)) [1]	⊕⊕⊕◯ MODERATE [2,4,5]	Low carbohydrate diet probably results in a small effect that may not be an important reduction in fasting glucose compared to a low fat diet
Change from baseline of fasting triglycerides Follow up: range 16 to 26 weeks	The mean change from baseline of fasting triglycerides ranged from -0.2 to 0.04 mmol/l	The mean change from baseline of fasting triglycerides in the low carb group was 0.22 mmol/l lower (-0.37, -0.08)	508 (6 RCTs (66,67,72,73,93,97))	⊕⊕⊕⊕ HIGH [6]	Low carbohydrate diet results in a small effect that may not be an important reduction in fasting triglycerides compared to a low fat diet
Change from baseline of fasting HDL Follow up: range 16 to 26 weeks	The mean change from baseline of fasting HDL ranged from -0.11 to -0.005 mmol/l	The mean change from baseline of fasting HDL in the low carb group was 0.09 mmol/l higher (-0.03, 0.22)	508 (6 RCTs (66,67,72,73,93,97))	⊕⊕◯◯ LOW [7,8]	Low carbohydrate diet may result in little to no difference in increase of fasting HDL compared to a low fat diet
Change from baseline of fasting LDL Follow up: range 16 to 26 weeks	The mean change from baseline of fasting LDL ranged from -0.25 to -0.04 mmol/l	The mean change from baseline of fasting LDL in the low carb group was 0.02 mmol/l higher (-0.09 0.13)	372 (5 RCTs (66,72,73,93,97))	⊕⊕⊕⊕ HIGH [9]	Low carbohydrate diet results in little to no difference in changes of fasting LDL compared to a low fat diet
Change from baseline of body weight Follow up: range 16 to 26 weeks	The mean change from baseline of body weight ranged from -11.5 to -1.4 kg	The mean change from baseline of body weight in the low carb group was 2.51 kg lower (-5.42, 0.4)	537 (7 RCTs (66,67,72,73,83,93,97)) [1]	⊕⊕◯◯ LOW [2,10,11]	Low carbohydrate diet may result in little to no difference in reduction of body weight compared to a low fat diet Both diets have considerable effects on body weight

Table 5 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of ≥ 16-26 weeks

Patient or population: people with type 2 diabetes. Data of ≥ 16-26 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change from baseline of BMI Follow up: range 16 to 26 weeks	The mean change from baseline of BMI ranged from -4 to -0.6 kg/m2	The mean change from baseline of BMI in the low carb group was 1.48 kg/m2 lower (-3.45, 0.49)	298 (5 RCTs (72,73,83,93,97)) [1]	⊕⊕◯◯ LOW [2,12,13]	Low carbohydrate diet may result in little to no difference in reduction of BMI compared to a low fat diet Both diets have considerable effects on BMI
Change from baseline of waist circumference Follow up: range 16 to 26 weeks	The mean change from baseline of waist circumference ranged from -9.1 to -4 cm	The mean change from baseline of waist circumference in the low carb group was 2.98 cm lower (-7.14, 1.18)	243 (3 RCTs (72,73,93))	⊕⊕⊕◯ MODERATE [13,14]	Low carbohydrate diet probably results in little to no difference in reduction of waist circumference compared to a low fat diet Both diets have considerable effects on waist circumference
Change from baseline of systolic blood pressure Follow up: mean 26 weeks	The mean change from baseline of systolic blood pressure ranged from -8.7 to -0.37 mmHg	The mean change from baseline of systolic blood pressure in the low carb group was 0.76 mmHg lower (-3.42, 1.9)	283 (4 RCTs (66,73,93,97))	⊕⊕⊕⊕ HIGH [15]	Low carbohydrate diet results in little to no difference in reduction of systolic blood pressure compared to a low fat diet The reduction in systolic blood pressure is clinically meaningful with both dietary interventions
Change from baseline of diastolic blood pressure Follow up: mean 26 weeks	The mean change from baseline of diastolic blood pressure ranged from -6.4 to 0.95 mmHg	The mean change from baseline of diastolic blood pressure in the intervention group was 1.91 mmHg lower (-3.63, -0.18)	283 (4 RCTs (66,73,93,97))	⊕⊕⊕◯ MODERATE [3]	Low carbohydrate diet probably results in a small effect that may not be an important reduction in diastolic blood pressure compared to a low fat diet The effect of both diets on diastolic blood pressure is of potential clinical significance
Change from baseline of quality of life Follow up: mean 26 weeks	In Guldbrand 2012 (73) the SF-36 was used, and in Yamada 2014 (97) the DTSQ and the PAID were used. But there was no difference in improvement of quality of life between the two diet groups with either of these instruments		69 (2 RCTs (73,97))	⊕⊕◯◯ LOW [16]	Low carbohydrate diet may result in little to no difference in improvement of quality of life compared to a low fat diet

CHO: Carbohydrates; CI: Confidence interval; vs: versus; Method of analysis for all outcomes: random effect (inverse variance)

Table 5 Low carbohydrate diet (≤ 40 en% CHO) compared to low fat diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of ≥ 16-26 weeks

Patient or population: people with type 2 diabetes. Data of ≥ 16-26 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low fat diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. One CCT
2. We did not downgrade for risk of bias for the CCT at serious risk of bias, as removing the study did not really alter the effect estimate
3. Downgraded one level for serious imprecision, the upper boundary of the CI is close to line of no difference, whilst the lower boundary of the CI indicates a clinical important difference
4. Downgraded one level for serious inconsistency ($I^2 = 71\%$)
5. We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of less than 3 mmol/l are not considered to be important. Therefore, the effect estimate is rather precise
6. We did not downgrade for imprecision. We considered reductions of less than 1 mmol/l not to be important to patients. Therefore, the effect estimate is rather precise
7. Downgraded one level for serious inconsistency ($I^2 = 91\%$)
8. Downgraded one level for serious imprecision. 95% CI includes both benefit of the low carb diet and no difference between the diets. We considered an increase of 0.1 mmol/l to be important
9. We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of less than 1 mmol/l are not considered to be important. Therefore, the effect estimate is rather precise
10. Downgraded one level for serious inconsistency ($I^2 = 88\%$)
11. Downgraded one level for serious imprecision. 95% CI includes both benefit of the low carb diet and no difference between the diets. We considered a reduction of 5% to be important (5-10 kilos in most studies)
12. Downgraded one level for serious inconsistency ($1^2 = 94\%$)
13. Downgraded one level for serious imprecision. 95% CI includes both benefit of the low carb diet and no difference between the diets
14. We did not downgrade for inconsistency. Although $I^2 = 82\%$, the 95% CI overlap, and we already downgraded for imprecision and decided not to downgrade twice
15. We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of less than 4 mmHg are not considered important. Therefore, the effect estimate is rather precise
16. Downgraded two levels for very serious imprecision, very low sample size

Table 6 Low carbohydrate diet (≤ 40 en% CHO) compared to low carbohydrate diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of > 26 weeks

Patient or population: people with type 2 diabetes. Data of > 26 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low carbohydrate diet (≤ 30 en% fat)

Outcomes	**Anticipated absolute effects (95% CI)**		**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Value with low fat diet (≤ 30 en% fat)	**Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet**			
Change from baseline of HbA1c Follow up: mean 52 weeks	The mean change from baseline of HbA1c ranged from -1.6 to 0.24 %	The mean change from baseline of HbA1c in the low carb group was 0.36 % lower (-0.58, -0.14)	390 (4 RCTs (66,68,73,96))	⊕⊕◯◯ LOW [1,2]	Low carbohydrate diet may result in a small effect that may not be an important reduction in HbA1c compared to a low fat diet A difference of 0.5% of HbA1c is considered to be clinically important
Change from baseline of fasting glucose Follow up: mean 52 weeks	The mean change from baseline of fasting glucose ranged from -4.9 to 0.4 mmol/l	The mean change from baseline of fasting glucose in the low carb group was 0.37 mmol/l lower (-1.22, 0.48)	340 (4 RCTs (68,75,89,96))	⊕⊕⊕◯ MODERATE [3,4,5]	Low carbohydrate diet probably results in little to no difference in changes of fasting glucose compared to a low fat diet Both diets had a potentially important impact on glucose levels
Change from baseline of fasting triglycerides Follow up: mean 52 weeks	The mean change from baseline of fasting triglycerides ranged from -0.88 to 0.3 mmol/l	The mean change from baseline of fasting triglycerides in the low carb group was 0.25 mmol/l lower (-0.47, -0.04)	468 (5 RCTs (66,68,73,75,96))	⊕⊕⊕◯ MODERATE [3,6,7]	Low carbohydrate diet probably results in a small effect that may not be an important reduction in fasting triglycerides compared to a low fat diet
Change from baseline of fasting HDL cholesterol Follow up: mean 52 weeks	The mean change from baseline of fasting HDL cholesterol ranged from -0.05 to 0.08 mmol/l	The mean change from baseline of fasting HDL cholesterol in the low carb group was 0.11 mmol/l higher (0.05, 0.18)	375 (4 RCTs (66,68,73,96))	⊕⊕◯◯ LOW [1,8,9]	Low carbohydrate may increase fasting HDL cholesterol slightly compared to a low fat diet
Change from baseline of fasting LDL Follow up: mean 52 weeks	The mean change from baseline in fasting LDL ranged from -0.37 to -0.1 mmol/l	The mean change from baseline in fasting LDL in the intervention group was 0.07 mmol/l lower (-0.23, 0.09)	375 (4 RCTs (66,68,73,96))	⊕⊕⊕⊕ HIGH [3,10]	Low carbohydrate diet results in little to no difference in reduction of fasting LDL compared to a low fat diet
Change from baseline of body weight Follow up: mean 52 weeks	The mean change from baseline of body weight ranged from -7.6 to 2.8 kg	The mean change from baseline of body weight in the low carb group was 0.19 kg lower (-1.65,1.27)	483 (5 RCTs (66,68,73,75,96))	⊕⊕⊕⊕ HIGH [3,11]	Low carbohydrate diet results in little to no difference in reduction of body weight compared to a low fat diet
Change from baseline of BMI Follow up: mean 52 weeks	The mean change from baseline of BMI ranged from -2.8 to -1.2 kg/m2	The mean change from baseline of BMI in the low carb group was 0.38 kg/m2 lower (-1.03, 0.27)	177 (2 RCTs (68,73))	⊕⊕⊕◯ MODERATE [1,12]	Low carbohydrate diet probably results in little to no difference in reduction of BMI compared to a low fat diet

Table 6 Low carbohydrate diet (≤ 40 en% CHO) compared to low carbohydrate diet (≤ 30 en% fat) for metabolic control in people with type 2 diabetes. Data of > 26 weeks

Patient or population: people with type 2 diabetes. Data of > 26 weeks
Intervention: low carbohydrate diet (≤ 40 en% CHO)
Comparison: low carbohydrate diet (≤ 30 en% fat)

Outcomes	Anticipated absolute effects (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Value with low fat diet (≤ 30 en% fat)	Difference low carbohydrate diet (≤ 40 en% CHO) vs low fat diet			
Change from baseline of waist circumference Follow up: mean 52 weeks	The mean change from baseline of waist circumference ranged from -9.1 to 6.6 cm	The mean change from baseline of waist circumference in the low carb group was 0.79 cm lower (-2.73, 1.15)	285 (3 RCTs (68,73,96))	⊕⊕⊕⊕ HIGH [3,12]	Low carbohydrate diet results in little to no difference in reduction of waist circumference compared to a low fat diet
Change from baseline of systolic blood pressure Follow up: mean 52 weeks	The mean change from baseline of systolic blood pressure ranged from -10 to 5 mmHg	The mean change from baseline of systolic blood pressure in the low carb group was 0.77 mmHg higher (-3.68, 5.21)	274 (3 RCTs (66,73,96))	⊕⊕⊕◯ MODERATE [13]	Low carbohydrate diet probably results in little to no difference in change of systolic blood pressure compared to a low fat diet
Change from baseline of diastolic blood pressure Follow up: mean 52 weeks	The mean change from baseline of diastolic blood pressure ranged from -8 to -1 mmHg	The mean change from baseline of diastolic blood pressure in the low carb group was 0.08 mmHg lower (-2.56, 2.39)	274 (3 RCTs (66,73,96))	⊕⊕◯◯ LOW [14]	Low carbohydrate diet may result in little to no difference in change of diastolic blood pressure compared to a low fat diet
Change from baseline of quality of life Assessed with: SF-36 Follow up: mean 52 weeks	The MD for physical component score (PCS) was 2.00 (95% CI -1.39 to 5.39; P = 0.25) and for the mental component score (MCS) 0.90 (SD 4.34) versus 1.10 (SD 6.11) with a MD of -0.20 (95% CI -2.99 to 2.59; P = 0.89).		55 (1 RCT (73))	⊕⊕◯◯ LOW [15]	Low carbohydrate diet may result in little to no difference in change of quality of life compared to a low fat diet

CHO: Carbohydrates; CI: Confidence interval; MD: Mean difference ; vs: versus; Method of analysis for all outcomes: random effect (inverse variance)

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level for serious risk of bias. One study was at high risk of bias and removing this study did alter the effect estimate
2. Downgraded one level for serious imprecision. Upper boundary of the CI is not clinically important
3. We did not downgrade for risk of bias for the study at high risk of bias, as removing the study did not really alter the effect estimate
4. Downgraded one level for serious inconsistency ($I^2 = 92\%$)
5. We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of less than 3 mmol/l are not considered to be important. Therefore, the effect estimate is rather precise
6. Downgraded one level for serious inconsistency ($I^2 = 73\%$)
7. We did not downgrade for imprecision. We considered reductions of less than 1 mmol/l not to be important to patients. Therefore, the effect estimate is rather precise and CI does not include

appreciable benefit or harm
8. We did not downgrade for inconsistency, as we already downgraded for risk of bias and imprecision
9. Downgraded one level for serious imprecision. 95% CI also includes no appreciable benefit
10. We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of less than 1 mmol/l are not considered to be important. Therefore, the effect estimate is rather precise
11. We did not downgrade for imprecision. 95% CI does not include appreciable harm or benefit. We considered a reduction of 5% to be important (5-10 kilos in most studies)
12. We did not downgrade for imprecision. 95% CI does not include appreciable harm of benefit
13. Downgraded one level for serious imprecision. The CI includes appreciable harm
14. Downgraded two levels for very serious imprecision. 95% CI includes both appreciable benefit and harm
15. Downgraded two levels for very serious imprecision. Very low sample size and wide CI

Legends for Figures

Figure 1: Study Flow diagram

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included randomized controlled trial

Plus signs denote low risk of bias; question marks denote unclear risk of bias; and minus signs denote high risk of bias.

Figure 3: Change from baseline of HbA1c

The forest plot (the graph on the right-hand side) has one line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the grey box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. IV, inverse variance.

Figure 4: Change from baseline of fasting glucose

The forest plot (the graph on the right-hand side) has one line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the grey box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. IV, inverse variance.

Figure 5: Change from baseline of fasting triglycerides

The forest plot (the graph on the right-hand side) has one line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the grey box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. IV, inverse variance.

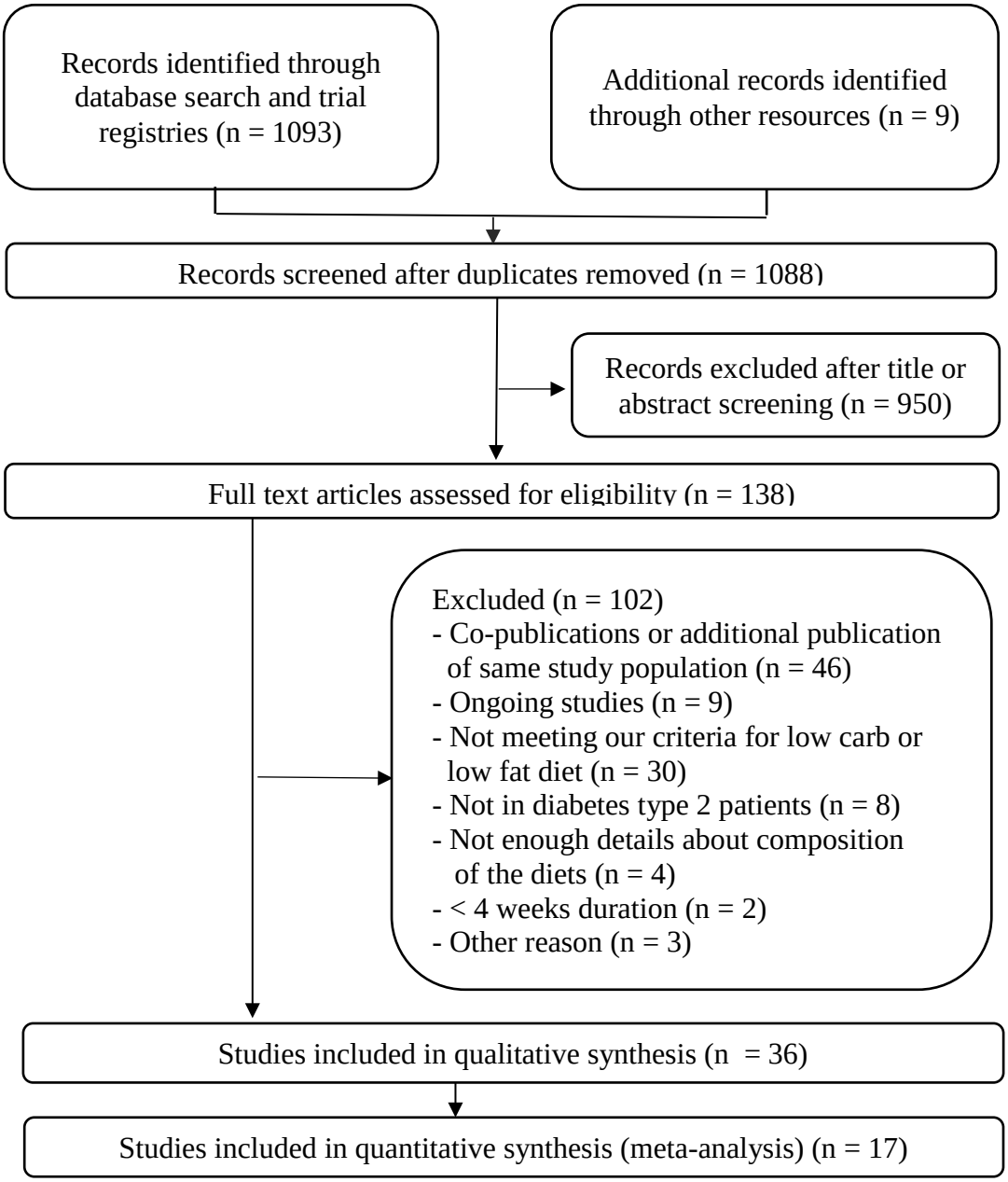
Figure 6: Change from baseline of Fasting HDL cholesterol

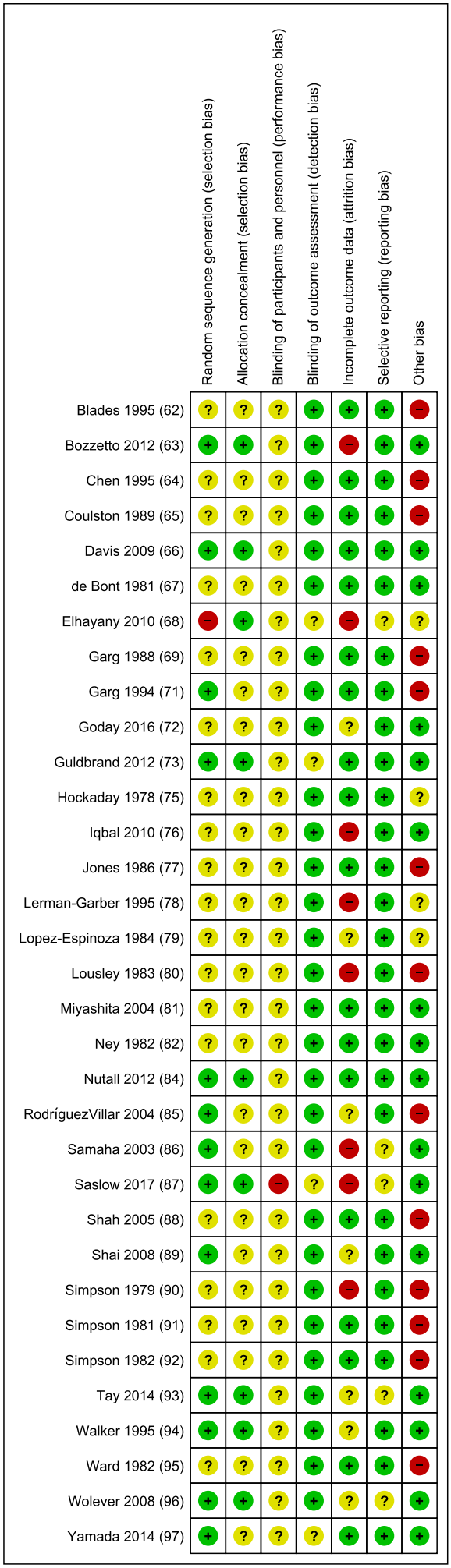
The forest plot (the graph on the right-hand side) has one line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the grey box on each

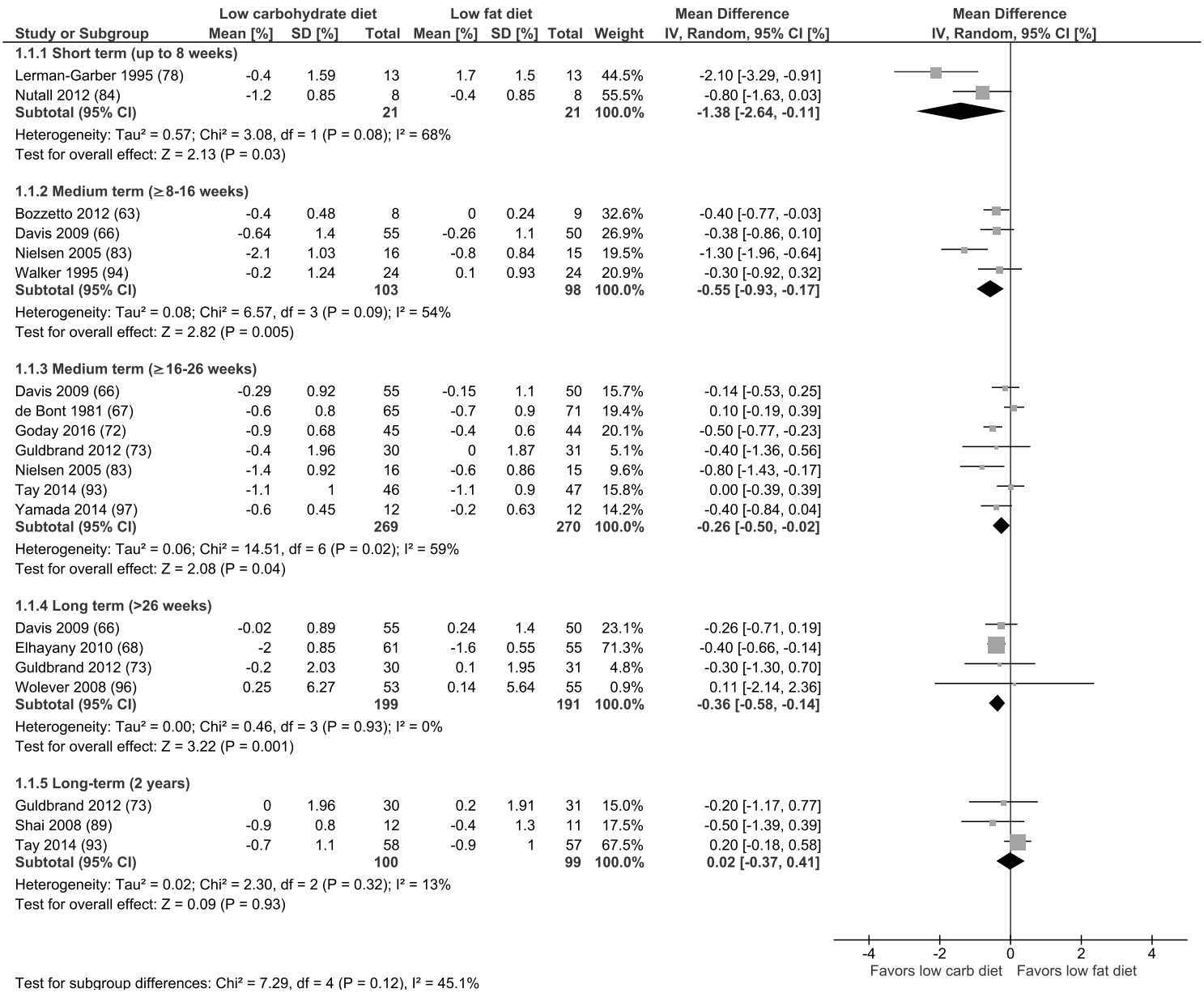
line). The black diamond at the bottom of each graph indicates the average effect size of the studies. IV, inverse variance.

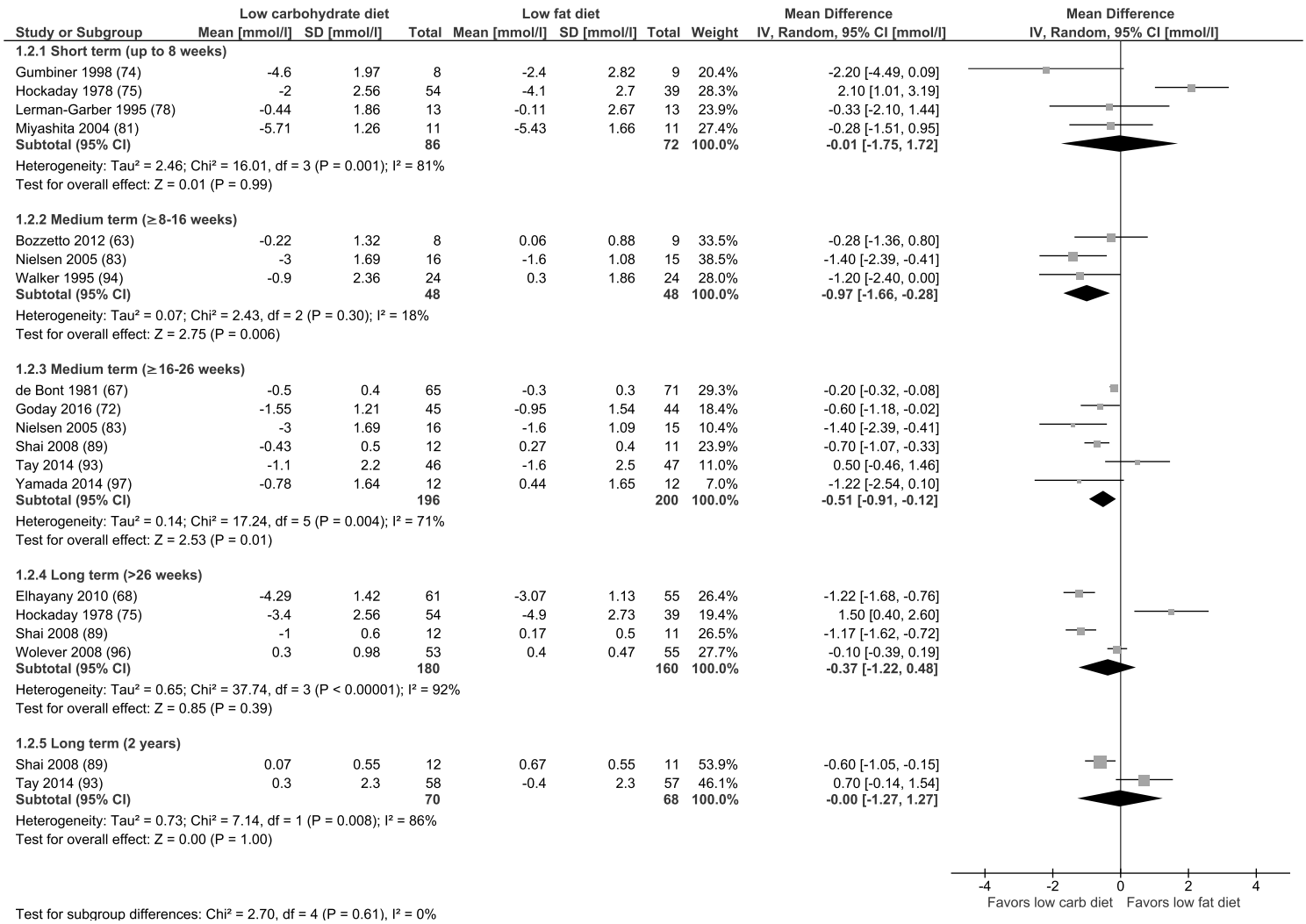
Figure 7: Change from baseline of fasting LDL cholesterol

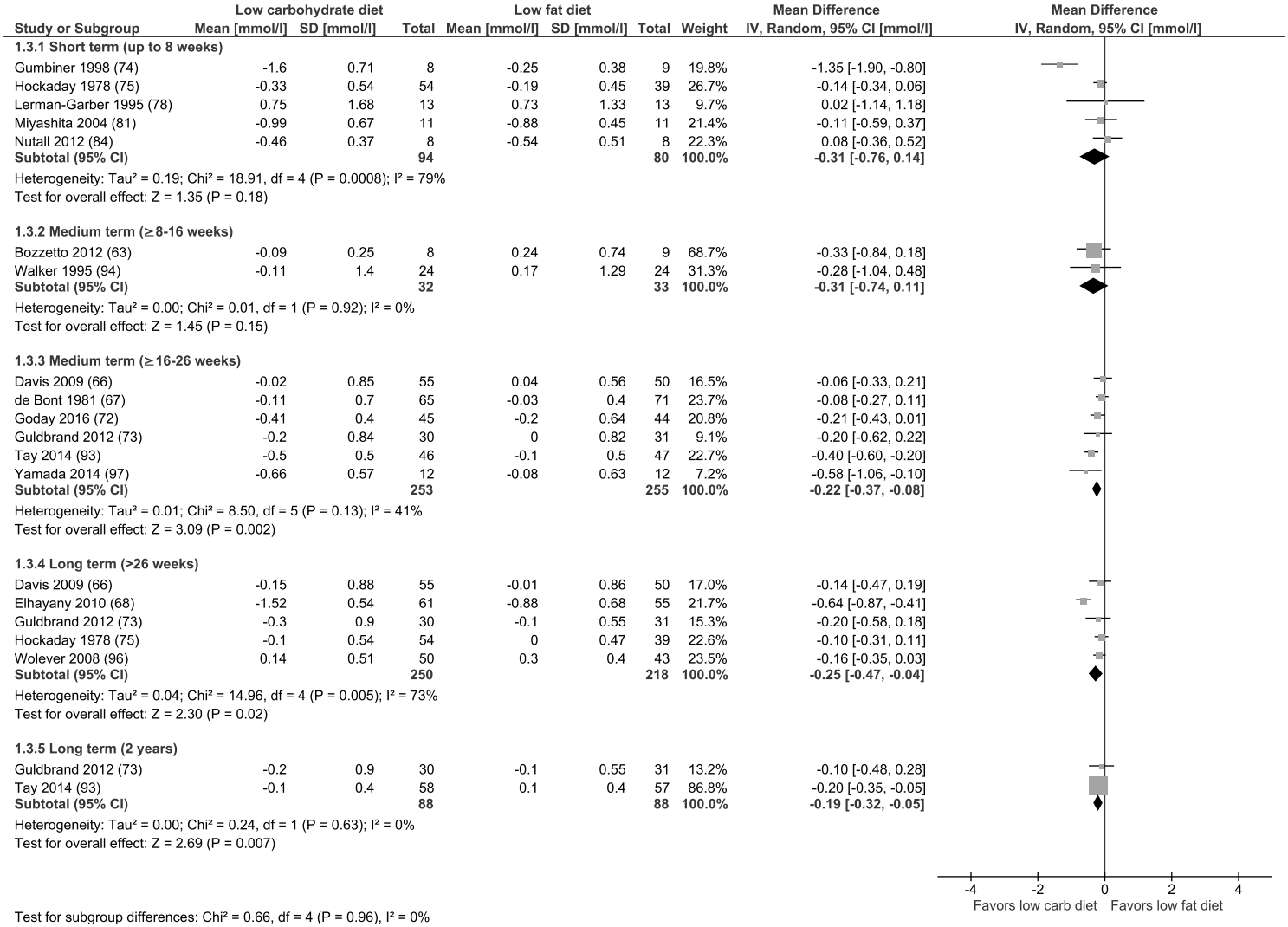
The forest plot (the graph on the right-hand side) has one line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the grey box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. IV, inverse variance.


Records identified through database search and trial registries (n = 1093)
Additional records identified through other resources (n = 9)
Records screened after duplicates removed (n = 1088)
Records excluded after title or abstract screening (n = 950)
Full text articles assessed for eligibility (n = 138)
Excluded (n = 102)
- Co-publications or additional publication of same study population (n = 46)
- Ongoing studies (n = 9)
- Not meeting our criteria for low carb or low fat diet (n = 30)
- Not in diabetes type 2 patients (n = 8)
- Not enough details about composition of the diets (n = 4)
- < 4 weeks duration (n = 2)
- Other reason (n = 3)
Studies included in qualitative synthesis (n = 36)
Studies included in quantitative synthesis (meta-analysis) (n = 17)

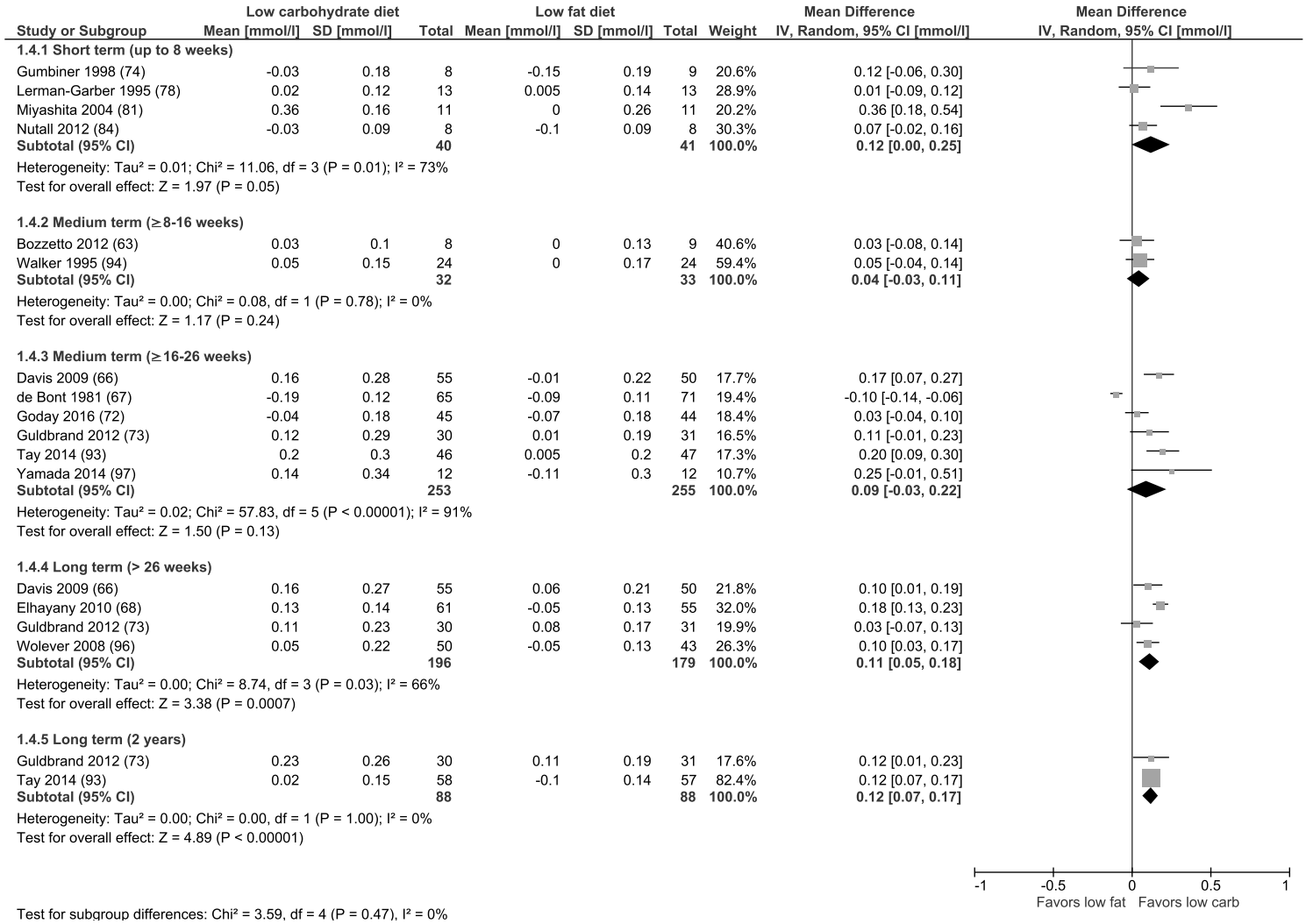

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Blades 1995 (62)
Bozzetto 2012 (63)
Chen 1995 (64)
Coulston 1989 (65)
Davis 2009 (66)
de Bont 1981 (67)
Elhayany 2010 (68)
Garg 1988 (69)
Garg 1994 (71)
Goday 2016 (72)
Guldbrand 2012 (73)
Hockaday 1978 (75)
Iqbal 2010 (76)
Jones 1986 (77)
Lerman-Garber 1995 (78)
Lopez-Espinoza 1984 (79)
Lousley 1983 (80)
Miyashita 2004 (81)
Ney 1982 (82)
Nutall 2012 (84)
RodríguezVillar 2004 (85)
Samaha 2003 (86)
Saslow 2017 (87)
Shah 2005 (88)
Shai 2008 (89)
Simpson 1979 (90)
Simpson 1981 (91)
Simpson 1982 (92)
Tay 2014 (93)
Walker 1995 (94)
Ward 1982 (95)
Wolever 2008 (96)
Yamada 2014 (97)

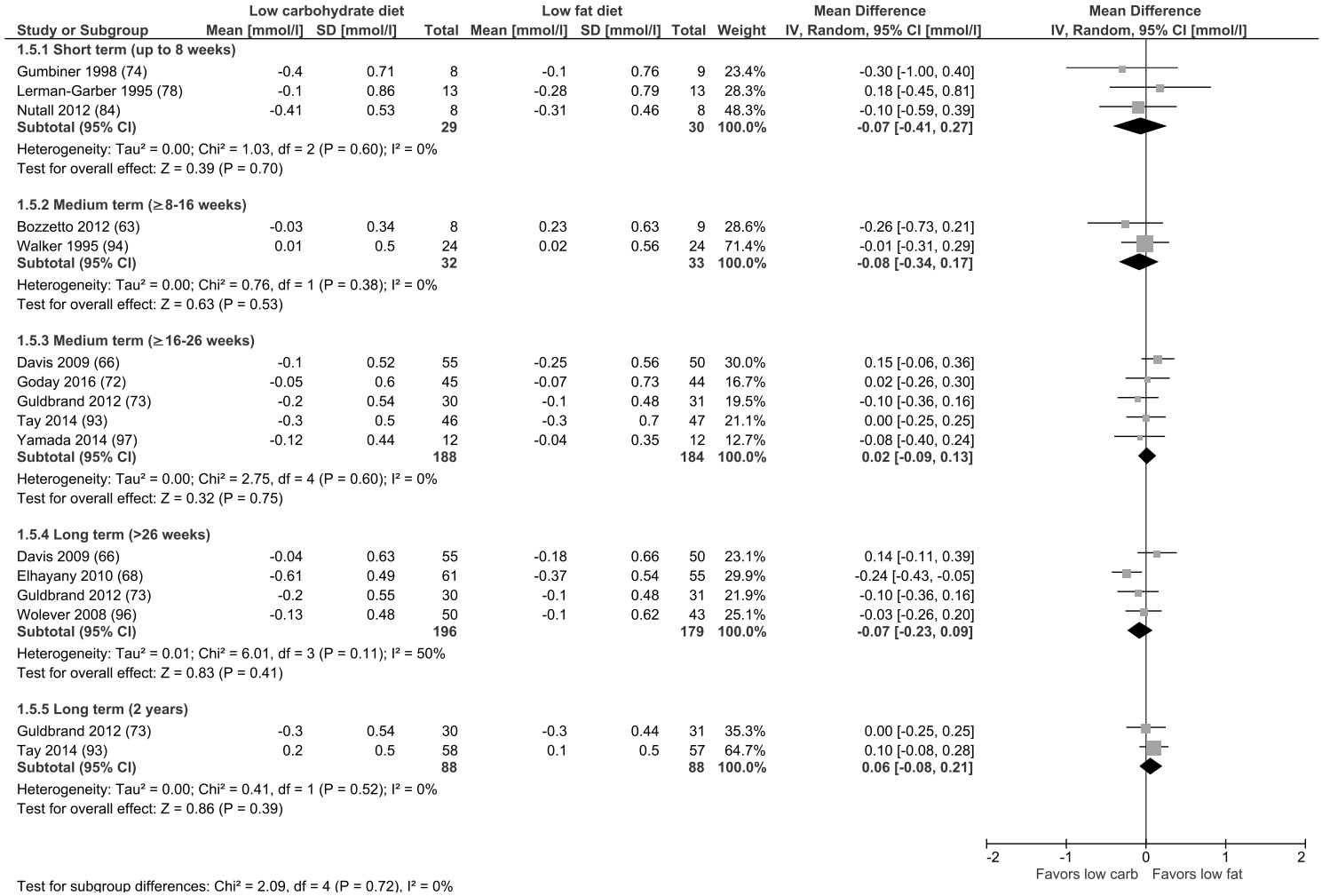

Low carbohydrate diet
Low fat diet
Mean Difference
Mean Difference
Study or Subgroup Mean [%] SD [%] Total Mean [%] SD [%] Total Weight IV, Random, 95% CI [%]
IV, Random, 95% CI [%]
1.1.1 Short term (up to 8 weeks)
Lerman-Garber 1995 (78) -0.4 1.59 13 1.7 1.5 13 44.5% -2.10 [-3.29, -0.91]
Nutall 2012 (84) -1.2 0.85 8 -0.4 0.85 8 55.5% -0.80 [-1.63, 0.03]
Subtotal (95% CI) 21 21 100.0% -1.38 [-2.64, -0.11]
Heterogeneity: Tau² = 0.57; Chi² = 3.08, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 2.13 (P = 0.03)
1.1.2 Medium term (≥8-16 weeks)
Bozzetto 2012 (63) -0.4 0.48 8 0 0.24 9 32.6% -0.40 [-0.77, -0.03]
Davis 2009 (66) -0.64 1.4 55 -0.26 1.1 50 26.9% -0.38 [-0.86, 0.10]
Nielsen 2005 (83) -2.1 1.03 16 -0.8 0.84 15 19.5% -1.30 [-1.96, -0.64]
Walker 1995 (94) -0.2 1.24 24 0.1 0.93 24 20.9% -0.30 [-0.92, 0.32]
Subtotal (95% CI) 103 98 100.0% -0.55 [-0.93, -0.17]
Heterogeneity: Tau² = 0.08; Chi² = 6.57, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 2.82 (P = 0.005)
1.1.3 Medium term (≥16-26 weeks)
Davis 2009 (66) -0.29 0.92 55 -0.15 1.1 50 15.7% -0.14 [-0.53, 0.25]
de Bont 1981 (67) -0.6 0.8 65 -0.7 0.9 71 19.4% 0.10 [-0.19, 0.39]
Goday 2016 (72) -0.9 0.68 45 -0.4 0.6 44 20.1% -0.50 [-0.77, -0.23]
Guldbrand 2012 (73) -0.4 1.96 30 0 1.87 31 5.1% -0.40 [-1.36, 0.56]
Nielsen 2005 (83) -1.4 0.92 16 -0.6 0.86 15 9.6% -0.80 [-1.43, -0.17]
Tay 2014 (93) -1.1 1 46 -1.1 0.9 47 15.8% 0.00 [-0.39, 0.39]
Yamada 2014 (97) -0.6 0.45 12 -0.2 0.63 12 14.2% -0.40 [-0.84, 0.04]
Subtotal (95% CI) 269 270 100.0% -0.26 [-0.50, -0.02]
Heterogeneity: Tau² = 0.06; Chi² = 14.51, df = 6 (P = 0.02); I² = 59%
Test for overall effect: Z = 2.08 (P = 0.04)
1.1.4 Long term (>26 weeks)
Davis 2009 (66) -0.02 0.89 55 0.24 1.4 50 23.1% -0.26 [-0.71, 0.19]
Elhayany 2010 (68) -2 0.85 61 -1.6 0.55 55 71.3% -0.40 [-0.66, -0.14]
Guldbrand 2012 (73) -0.2 2.03 30 0.1 1.95 31 4.8% -0.30 [-1.30, 0.70]
Wolever 2008 (96) 0.25 6.27 53 0.14 5.64 55 0.9% 0.11 [-2.14, 2.36]
Subtotal (95% CI) 199 191 100.0% -0.36 [-0.58, -0.14]
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 3 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)
1.1.5 Long-term (2 years)
Guldbrand 2012 (73) 0 1.96 30 0.2 1.91 31 15.0% -0.20 [-1.17, 0.77]
Shai 2008 (89) -0.9 0.8 12 -0.4 1.3 11 17.5% -0.50 [-1.39, 0.39]
Tay 2014 (93) -0.7 1.1 58 -0.9 1 57 67.5% 0.20 [-0.18, 0.58]
Subtotal (95% CI) 100 99 100.0% 0.02 [-0.37, 0.41]
Heterogeneity: Tau² = 0.02; Chi² = 2.30, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 0.09 (P = 0.93)
-4
-2
0
2
4
Favors low carb diet
Favors low fat diet
Test for subgroup differences: Chi² = 7.29, df = 4 (P = 0.12), I² = 45.1%


Low carbohydrate diet
Low fat diet
Mean Difference
Mean Difference
Study or Subgroup Mean [mmol/l] SD [mmol/l] Total Mean [mmol/l] SD [mmol/l] Total Weight IV, Random, 95% CI [mmol/l]
IV, Random, 95% CI [mmol/l]
1.2.1 Short term (up to 8 weeks)
Gumbiner 1998 (74) -4.6 1.97 8 -2.4 2.82 9 20.4% -2.20 [-4.49, 0.09]
Hockaday 1978 (75) -2 2.56 54 -4.1 2.7 39 28.3% 2.10 [1.01, 3.19]
Lerman-Garber 1995 (78) -0.44 1.86 13 -0.11 2.67 13 23.9% -0.33 [-2.10, 1.44]
Miyashita 2004 (81) -5.71 1.26 11 -5.43 1.66 11 27.4% -0.28 [-1.51, 0.95]
Subtotal (95% CI) 86 72 100.0% -0.01 [-1.75, 1.72]
Heterogeneity: Tau² = 2.46; Chi² = 16.01, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 0.01 (P = 0.99)
1.2.2 Medium term (≥8-16 weeks)
Bozzetto 2012 (63) -0.22 1.32 8 0.06 0.88 9 33.5% -0.28 [-1.36, 0.80]
Nielsen 2005 (83) -3 1.69 16 -1.6 1.08 15 38.5% -1.40 [-2.39, -0.41]
Walker 1995 (94) -0.9 2.36 24 0.3 1.86 24 28.0% -1.20 [-2.40, 0.00]
Subtotal (95% CI) 48 48 100.0% -0.97 [-1.66, -0.28]
Heterogeneity: Tau² = 0.07; Chi² = 2.43, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.75 (P = 0.006)
1.2.3 Medium term (≥16-26 weeks)
de Bont 1981 (67) -0.5 0.4 65 -0.3 0.3 71 29.3% -0.20 [-0.32, -0.08]
Goday 2016 (72) -1.55 1.21 45 -0.95 1.54 44 18.4% -0.60 [-1.18, -0.02]
Nielsen 2005 (83) -3 1.69 16 -1.6 1.09 15 10.4% -1.40 [-2.39, -0.41]
Shai 2008 (89) -0.43 0.5 12 0.27 0.4 11 23.9% -0.70 [-1.07, -0.33]
Tay 2014 (93) -1.1 2.2 46 -1.6 2.5 47 11.0% 0.50 [-0.46, 1.46]
Yamada 2014 (97) -0.78 1.64 12 0.44 1.65 12 7.0% -1.22 [-2.54, 0.10]
Subtotal (95% CI) 196 200 100.0% -0.51 [-0.91, -0.12]
Heterogeneity: Tau² = 0.14; Chi² = 17.24, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 2.53 (P = 0.01)
1.2.4 Long term (>26 weeks)
Elhayany 2010 (68) -4.29 1.42 61 -3.07 1.13 55 26.4% -1.22 [-1.68, -0.76]
Hockaday 1978 (75) -3.4 2.56 54 -4.9 2.73 39 19.4% 1.50 [0.40, 2.60]
Shai 2008 (89) -1 0.6 12 0.17 0.5 11 26.5% -1.17 [-1.62, -0.72]
Wolever 2008 (96) 0.3 0.98 53 0.4 0.47 55 27.7% -0.10 [-0.39, 0.19]
Subtotal (95% CI) 180 160 100.0% -0.37 [-1.22, 0.48]
Heterogeneity: Tau² = 0.65; Chi² = 37.74, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.85 (P = 0.39)
1.2.5 Long term (2 years)
Shai 2008 (89) 0.07 0.55 12 0.67 0.55 11 53.9% -0.60 [-1.05, -0.15]
Tay 2014 (93) 0.3 2.3 58 -0.4 2.3 57 46.1% 0.70 [-0.14, 1.54]
Subtotal (95% CI) 70 68 100.0% -0.00 [-1.27, 1.27]
Heterogeneity: Tau² = 0.73; Chi² = 7.14, df = 1 (P = 0.008); I² = 86%
Test for overall effect: Z = 0.00 (P = 1.00)
-4
-2
0
2
4
Favors low carb diet
Favors low fat diet
Test for subgroup differences: Chi² = 2.70, df = 4 (P = 0.61), I² = 0%



Test for subgroup differences: Chi² = 0.66, df = 4 (P = 0.96), I² = 0%


Low carbohydrate diet
Low fat diet
Mean Difference
Mean Difference
Study or Subgroup
Mean [mmol/l] SD [mmol/l] Total Mean [mmol/l] SD [mmol/l] Total Weight IV, Random, 95% CI [mmol/l]
IV, Random, 95% CI [mmol/l]
1.4.1 Short term (up to 8 weeks)
Gumbiner 1998 (74) -0.03 0.18 8 -0.15 0.19 9 20.6% 0.12 [-0.06, 0.30]
Lerman-Garber 1995 (78) 0.02 0.12 13 0.005 0.14 13 28.9% 0.01 [-0.09, 0.12]
Miyashita 2004 (81) 0.36 0.16 11 0 0.26 11 20.2% 0.36 [0.18, 0.54]
Nutall 2012 (84) -0.03 0.09 8 -0.1 0.09 8 30.3% 0.07 [-0.02, 0.16]
Subtotal (95% CI) 40 41 100.0% 0.12 [0.00, 0.25]
Heterogeneity: Tau² = 0.01; Chi² = 11.06, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 1.97 (P = 0.05)
1.4.2 Medium term (≥8-16 weeks)
Bozzetto 2012 (63) 0.03 0.1 8 0 0.13 9 40.6% 0.03 [-0.08, 0.14]
Walker 1995 (94) 0.05 0.15 24 0 0.17 24 59.4% 0.05 [-0.04, 0.14]
Subtotal (95% CI) 32 33 100.0% 0.04 [-0.03, 0.11]
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)
1.4.3 Medium term (≥16-26 weeks)
Davis 2009 (66) 0.16 0.28 55 -0.01 0.22 50 17.7% 0.17 [0.07, 0.27]
de Bont 1981 (67) -0.19 0.12 65 -0.09 0.11 71 19.4% -0.10 [-0.14, -0.06]
Goday 2016 (72) -0.04 0.18 45 -0.07 0.18 44 18.4% 0.03 [-0.04, 0.10]
Guldbrand 2012 (73) 0.12 0.29 30 0.01 0.19 31 16.5% 0.11 [-0.01, 0.23]
Tay 2014 (93) 0.2 0.3 46 0.005 0.2 47 17.3% 0.20 [0.09, 0.30]
Yamada 2014 (97) 0.14 0.34 12 -0.11 0.3 12 10.7% 0.25 [-0.01, 0.51]
Subtotal (95% CI) 253 255 100.0% 0.09 [-0.03, 0.22]
Heterogeneity: Tau² = 0.02; Chi² = 57.83, df = 5 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.50 (P = 0.13)
1.4.4 Long term (> 26 weeks)
Davis 2009 (66) 0.16 0.27 55 0.06 0.21 50 21.8% 0.10 [0.01, 0.19]
Elhayany 2010 (68) 0.13 0.14 61 -0.05 0.13 55 32.0% 0.18 [0.13, 0.23]
Guldbrand 2012 (73) 0.11 0.23 30 0.08 0.17 31 19.9% 0.03 [-0.07, 0.13]
Wolever 2008 (96) 0.05 0.22 50 -0.05 0.13 43 26.3% 0.10 [0.03, 0.17]
Subtotal (95% CI) 196 179 100.0% 0.11 [0.05, 0.18]
Heterogeneity: Tau² = 0.00; Chi² = 8.74, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 3.38 (P = 0.0007)
1.4.5 Long term (2 years)
Guldbrand 2012 (73) 0.23 0.26 30 0.11 0.19 31 17.6% 0.12 [0.01, 0.23]
Tay 2014 (93) 0.02 0.15 58 -0.1 0.14 57 82.4% 0.12 [0.07, 0.17]
Subtotal (95% CI) 88 88 100.0% 0.12 [0.07, 0.17]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 4.89 (P < 0.00001)
-1
-0.5
0
0.5
1
Favors low fat
Favors low carb
Test for subgroup differences: Chi² = 3.59, df = 4 (P = 0.47), I² = 0%

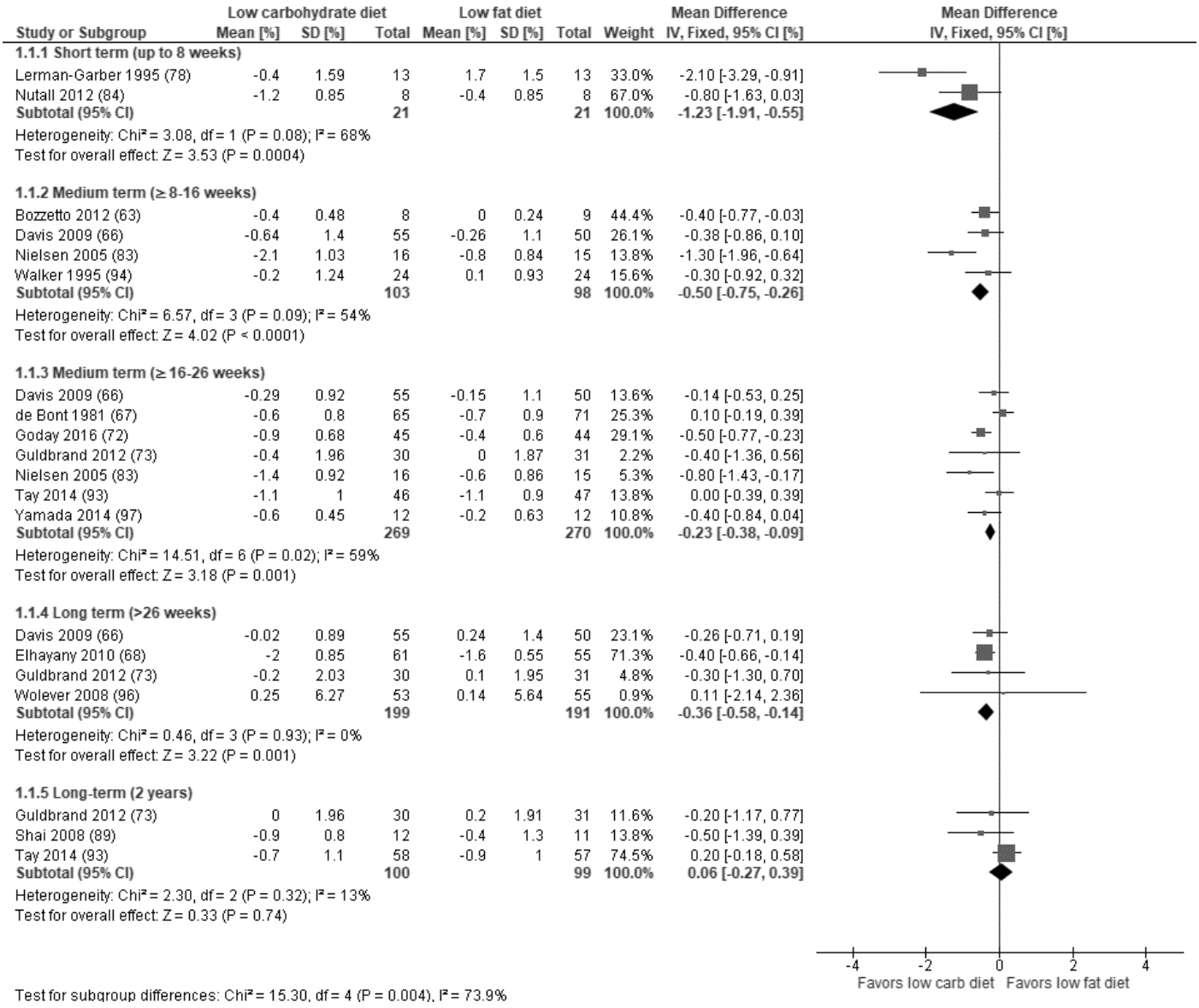


Test for subgroup differences: Chi² = 2.09, df = 4 (P = 0.72), I² = 0%

Online Supporting Material (OSM) – Supplemental Figure 1

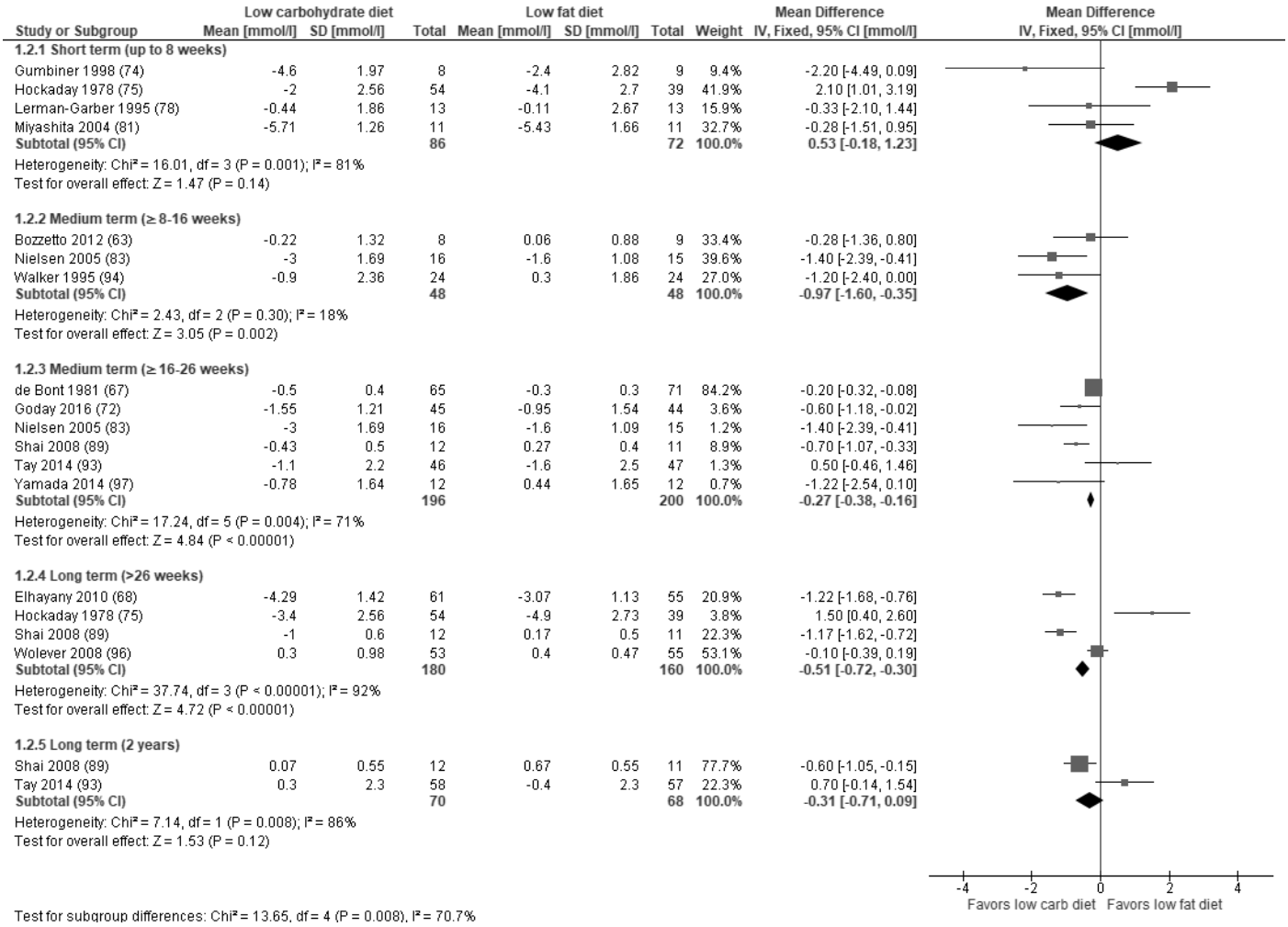
Supplemental Figure 1 Sensitivity analyses using the fixed-effects model per outcome (Figure 1a-1j)

Figure 1a Change from baseline of HbA1c



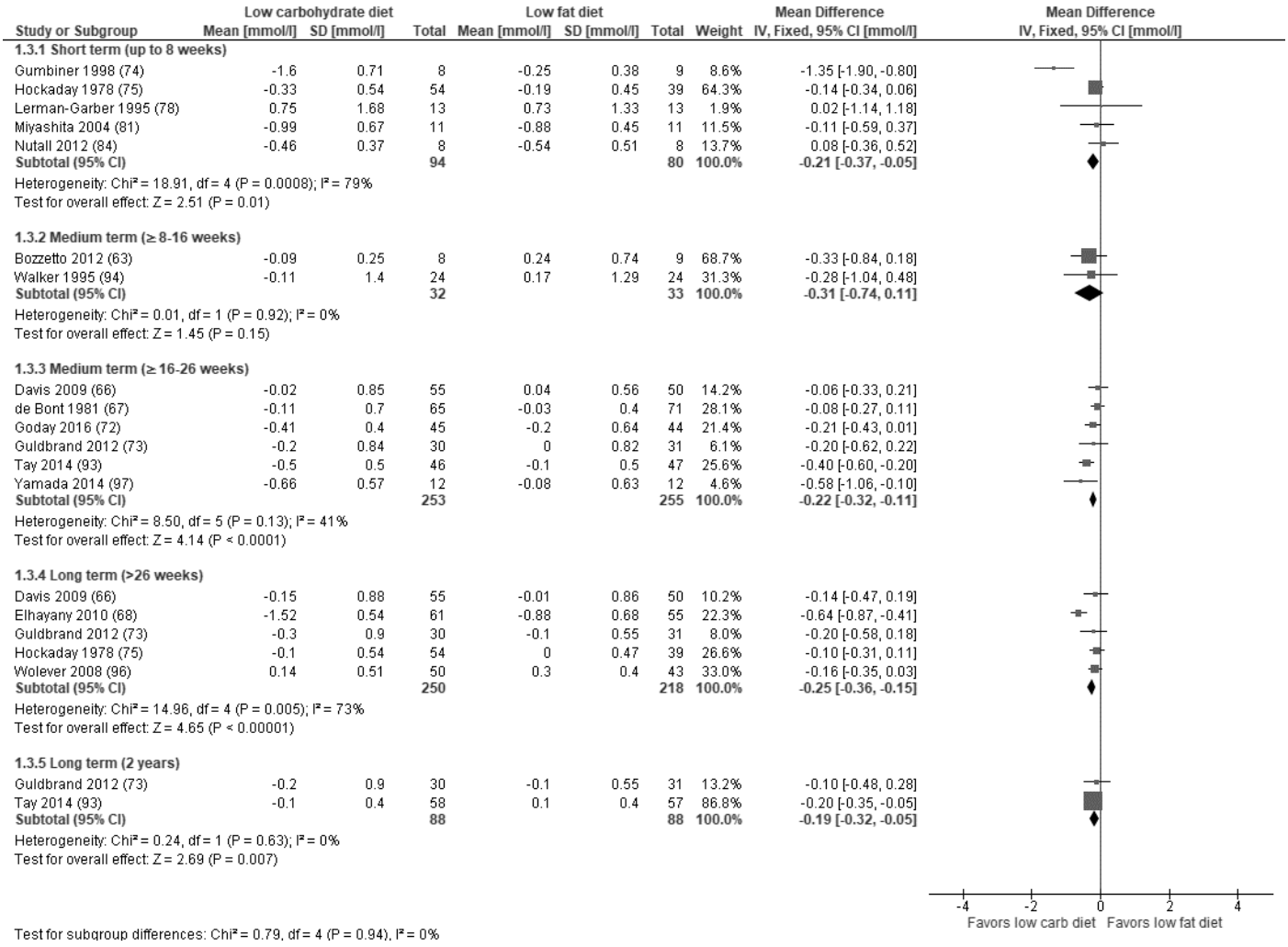
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1b Change from baseline of fasting glucose



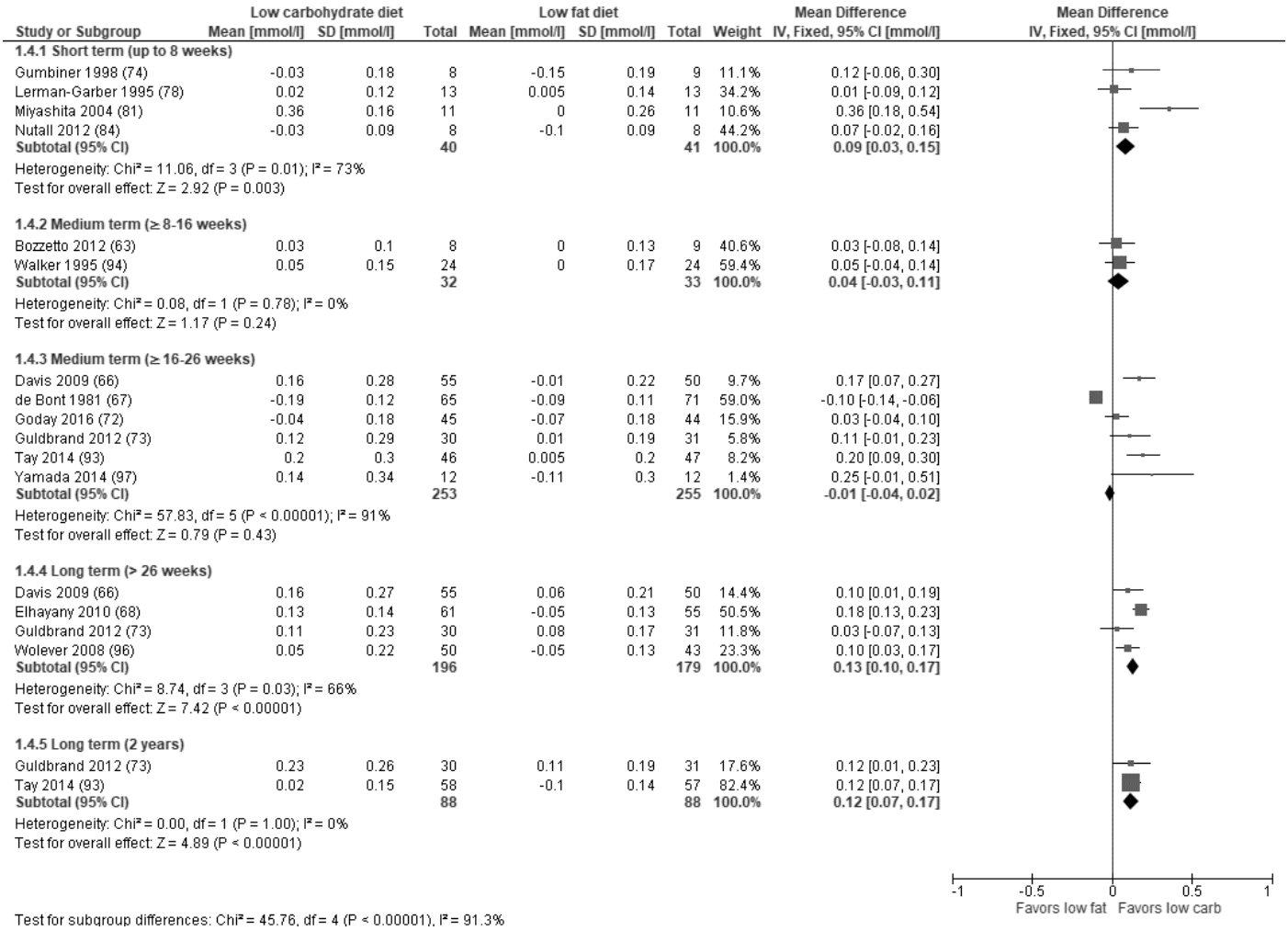
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1c Change from baseline of fasting triglycerides



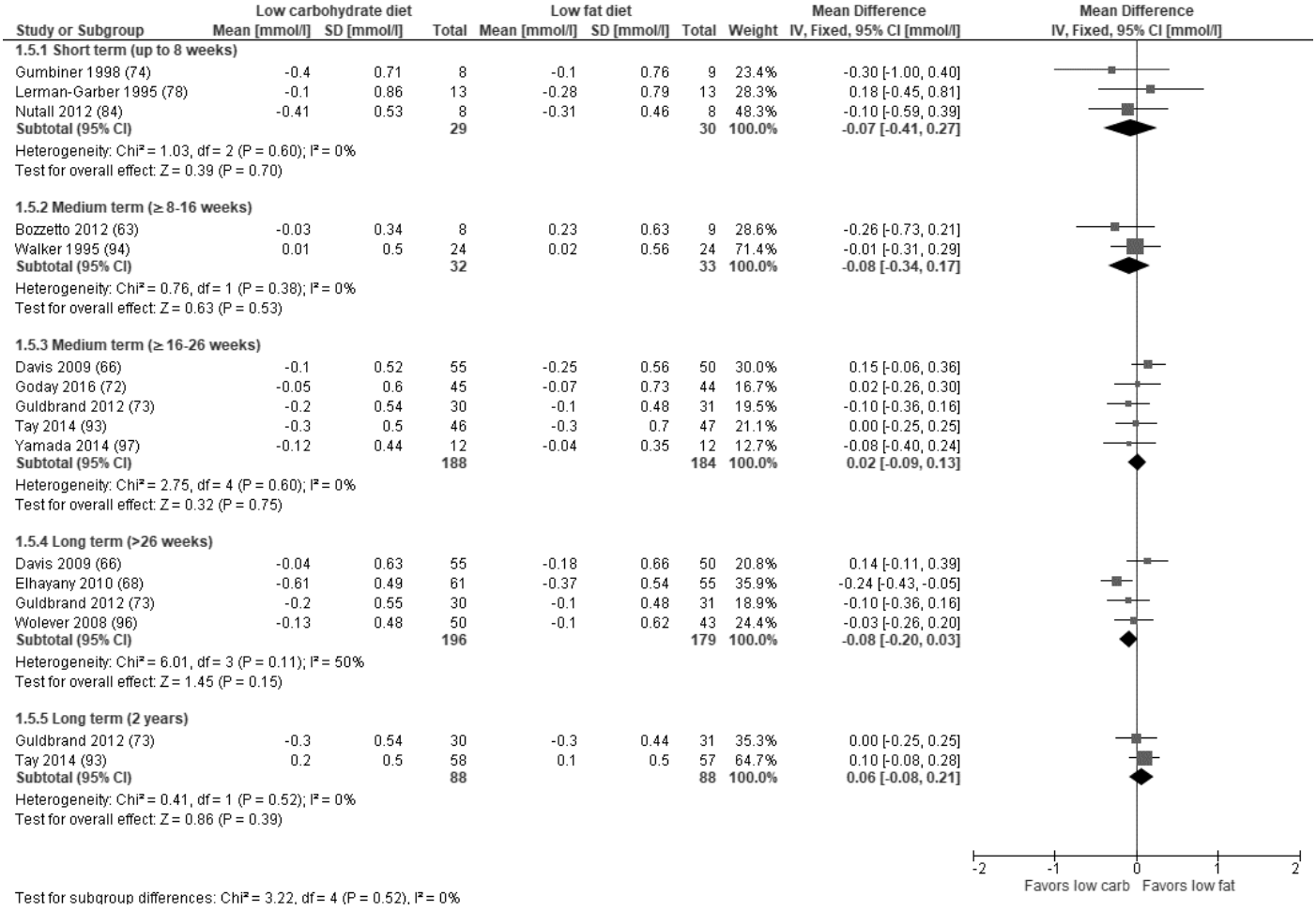
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1d Change from baseline of fasting HDL cholesterol



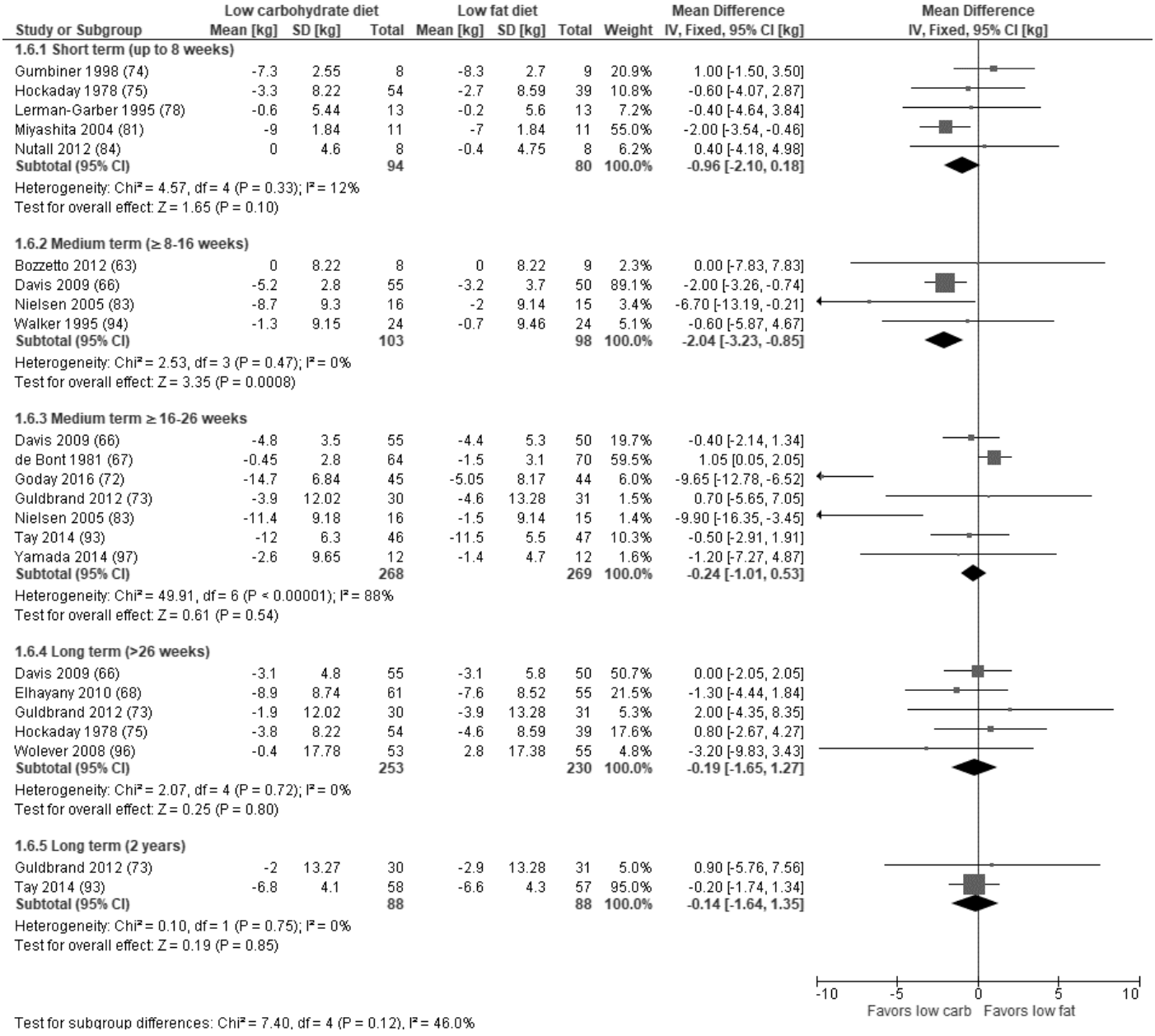
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1e Change from baseline of fasting LDL cholesterol



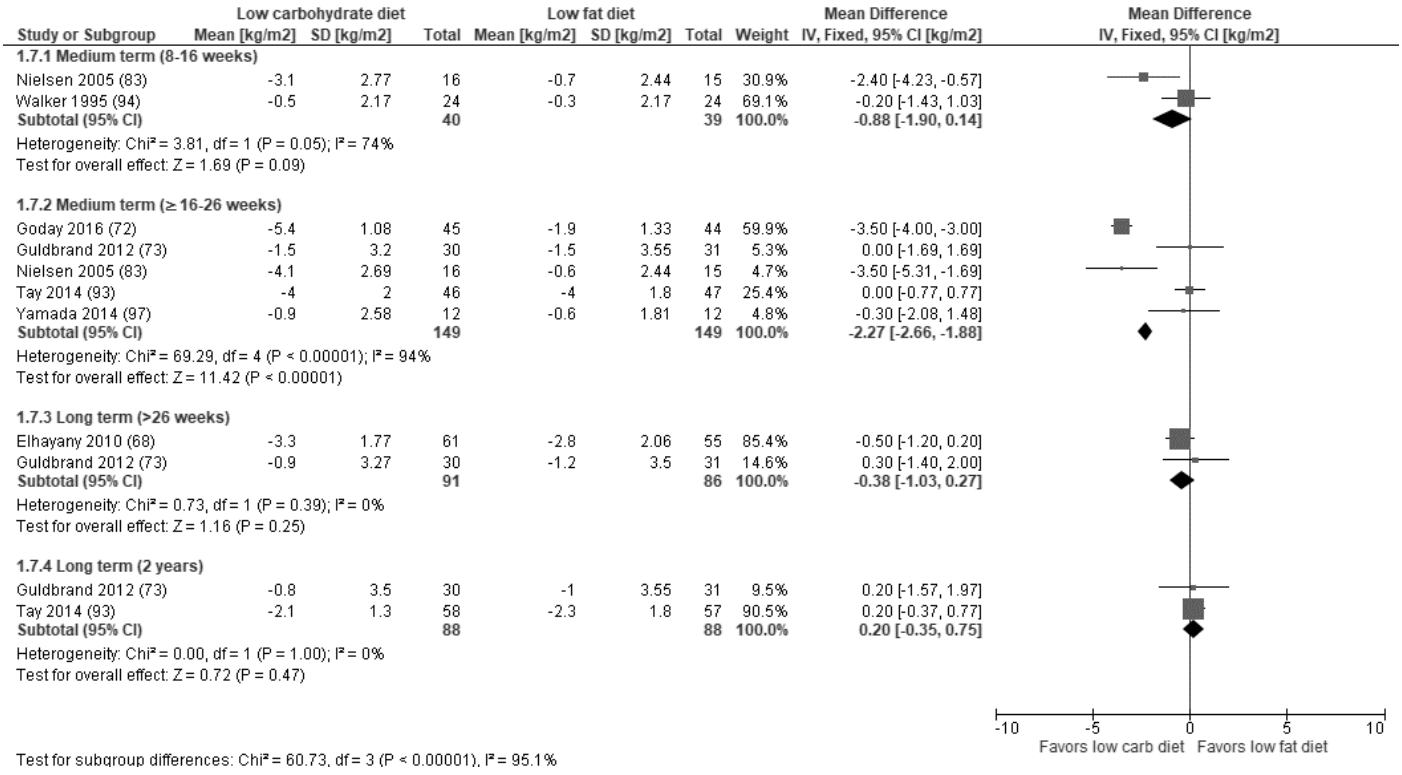
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1f Change from baseline of body weight



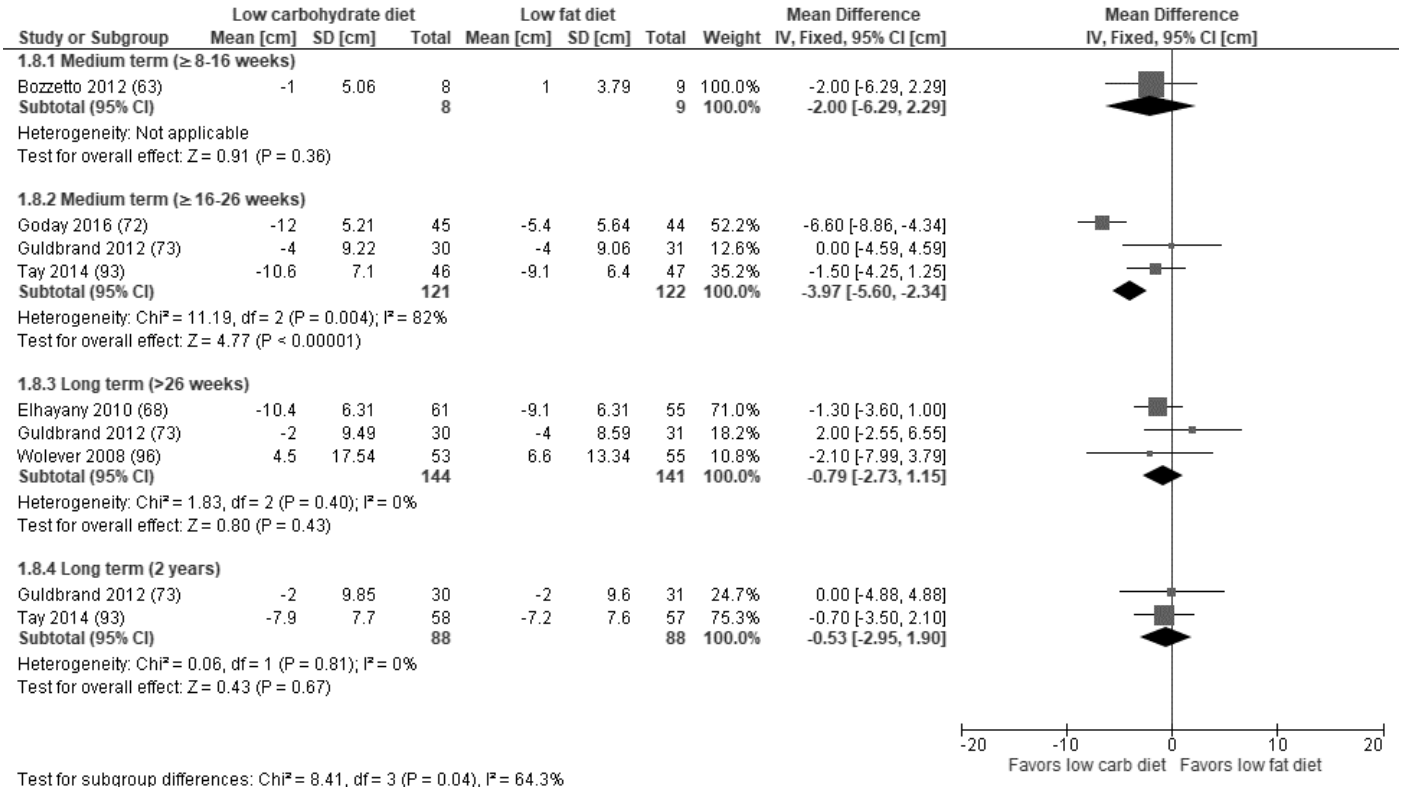
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1g Change from baseline of BMI



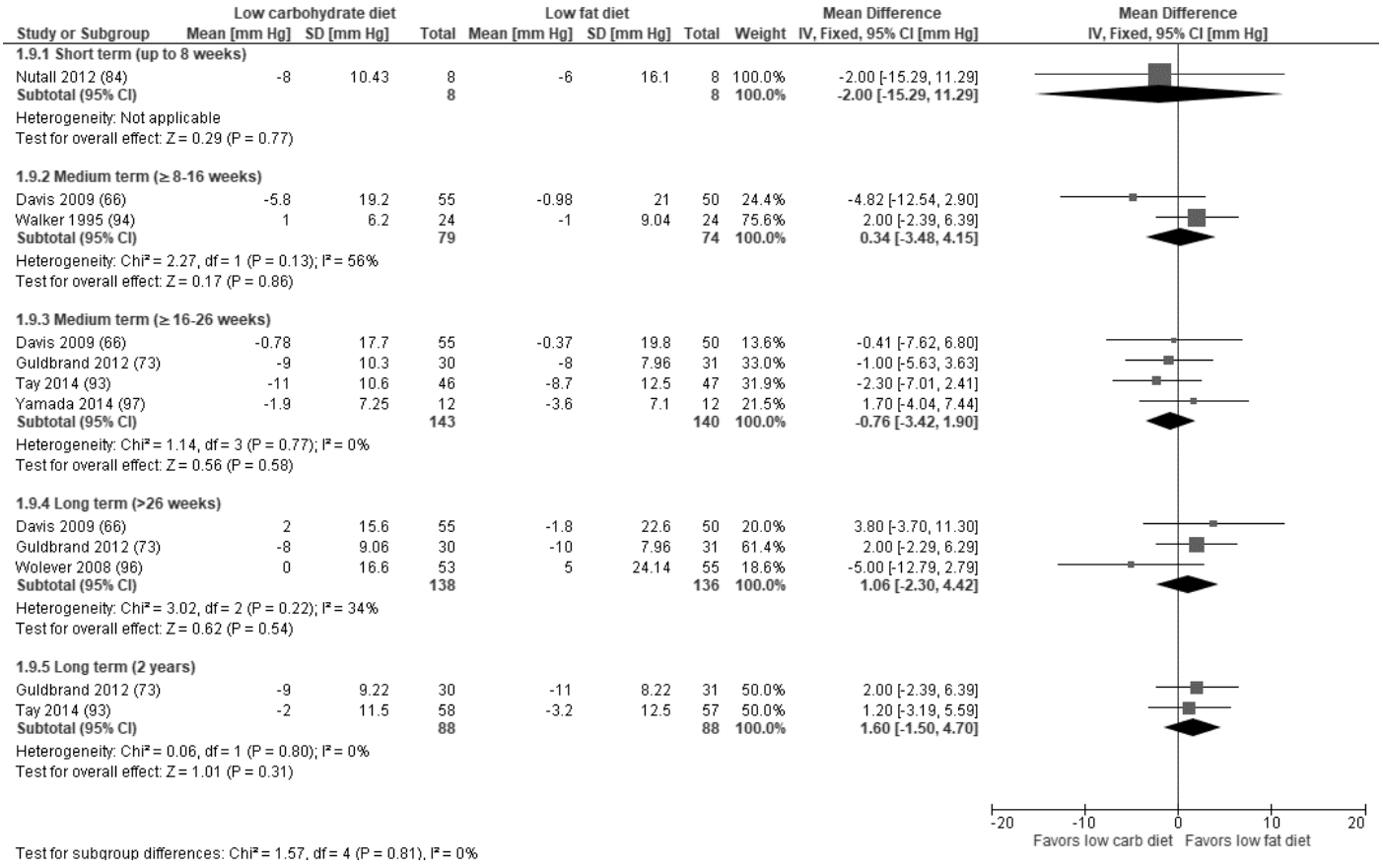
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1h Change from baseline of waist circumference



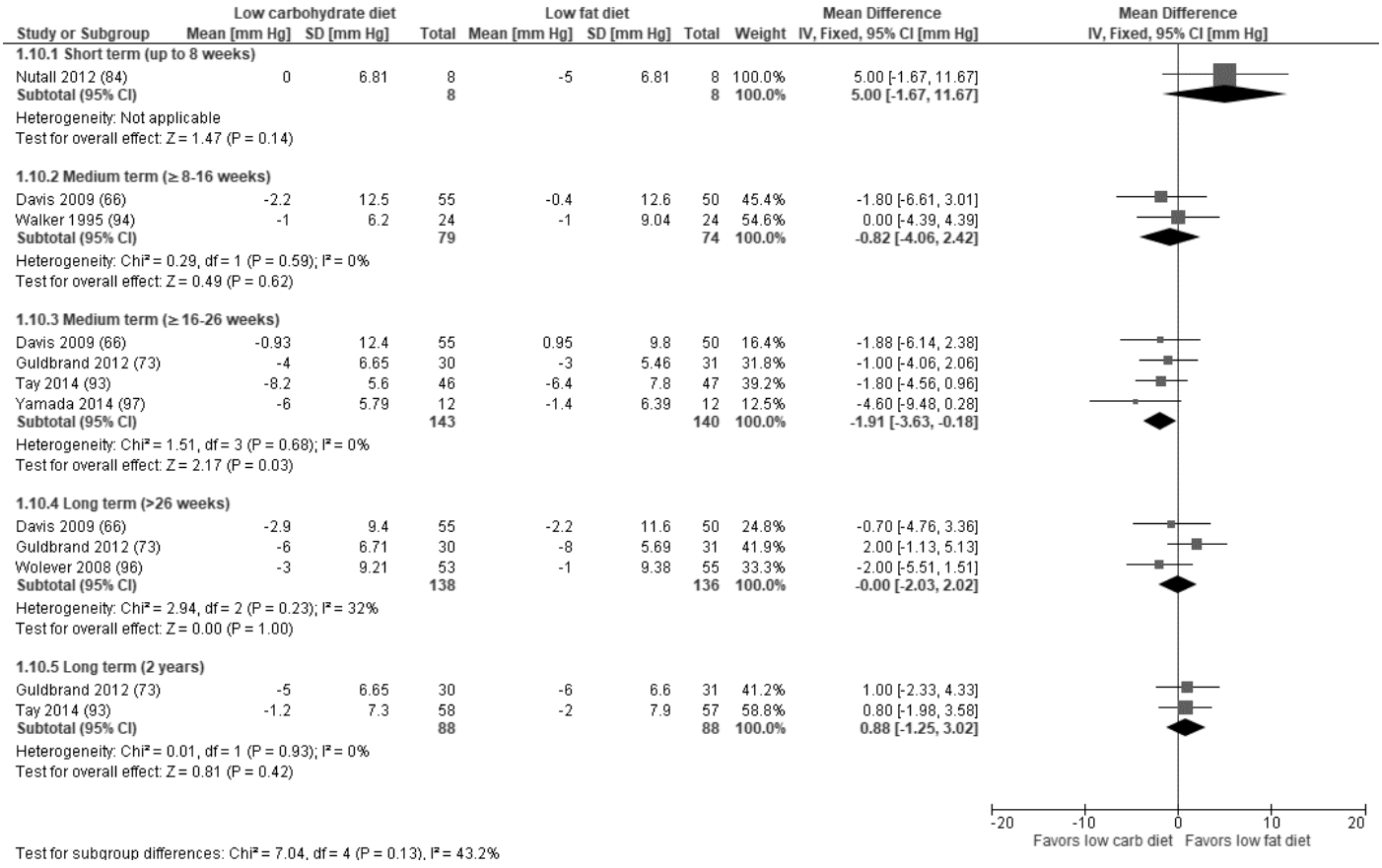
Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1iChange from baseline of systolic blood pressure



Online Supporting Material (OSM) – Supplemental Figure 1

Figure 1j Change from baseline of diastolic blood pressure



Supplemental Figure 2 Sensitivity analyses Removing RCTs at 'high risk of bias' or CCT at 'serious risk of bias' per outcome (Figure 2a-2h)

Figure 2a Change from baseline of HbA1c, without Lerman-Garber 1995 (78) in 1.1.1, Bozzetto 2012 (63) in 1.1.2, Elhayany 2010 (68) in data and analysis 1.1.4, and Nielsen 2005 (83) in data and analyses 1.1.2 and 1.1.3

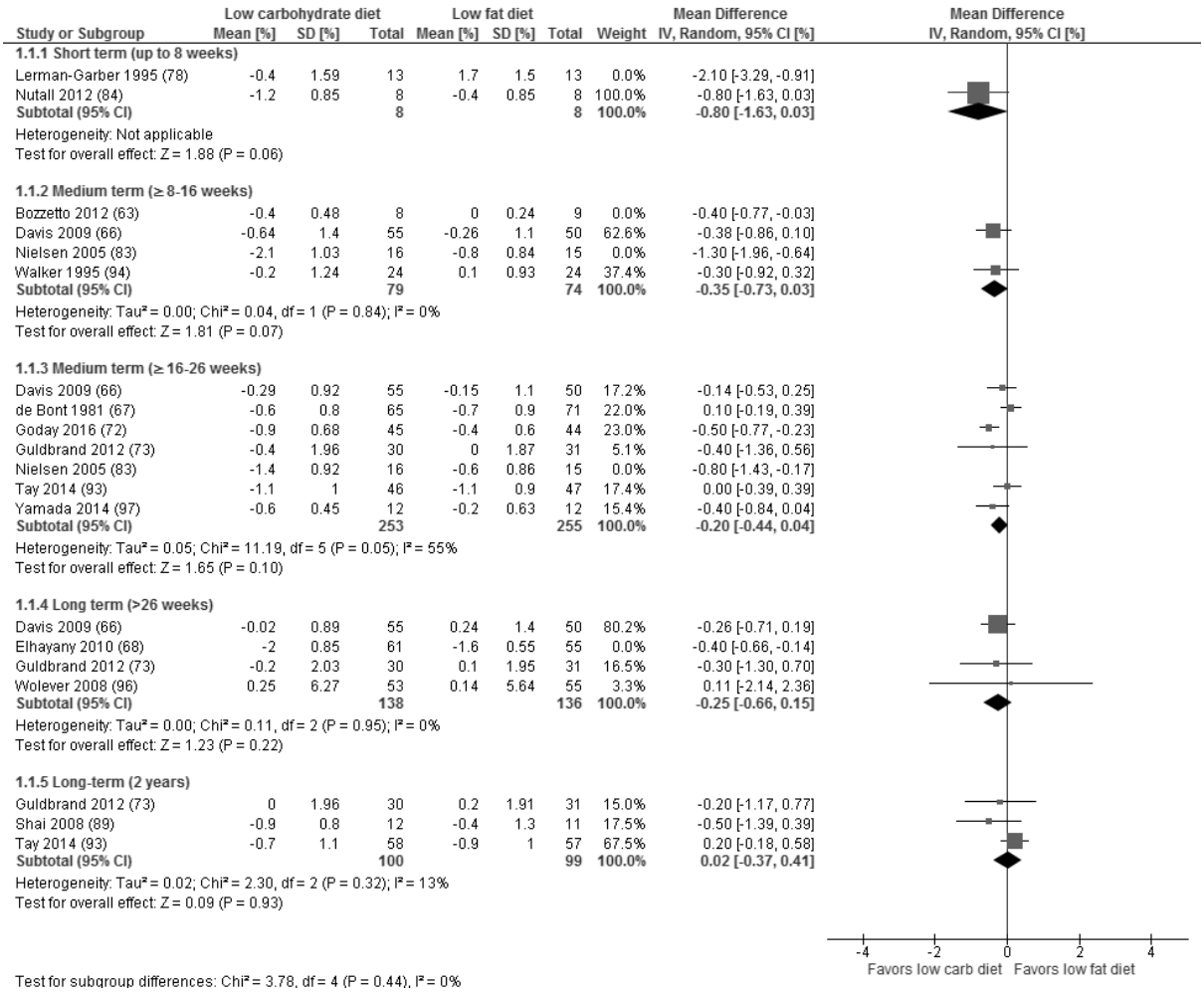


Figure 2b Change from baseline of fasting glucose, without Lerman-Garber 1995 (78) in data and analysis 1.2.1, Bozzetto 2012 (63) in 1.2.2, Elhayany 2010 (68) in 1.2.4, and Nielsen 2005 (83) in 1.2.2 and 1.2.3

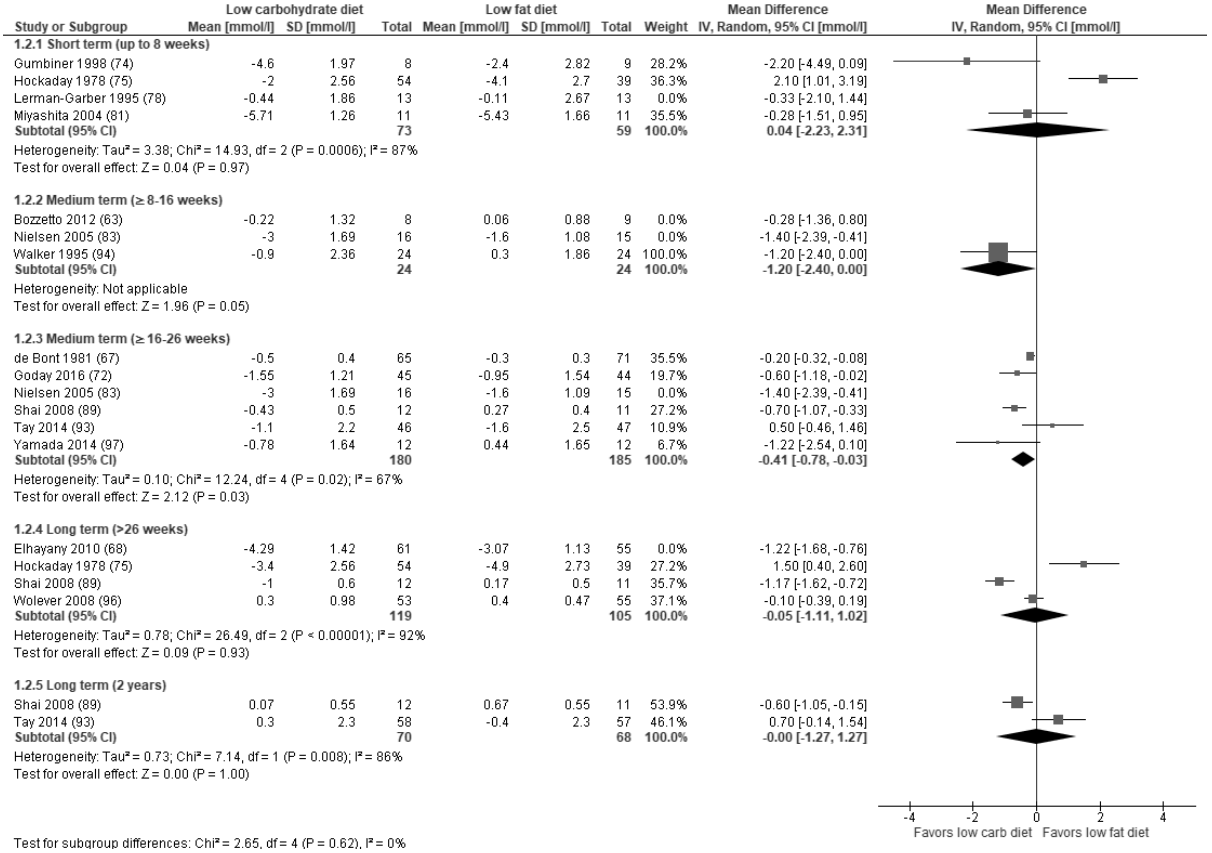


Figure 2c Change from baseline of fasting triglycerides, without Lerman-Garber 1995 (78) in data and analysis 1.3.1, Bozzetto 2012 (63) in 1.3.2, and Elhayany 2010 (68) in 1.3.4

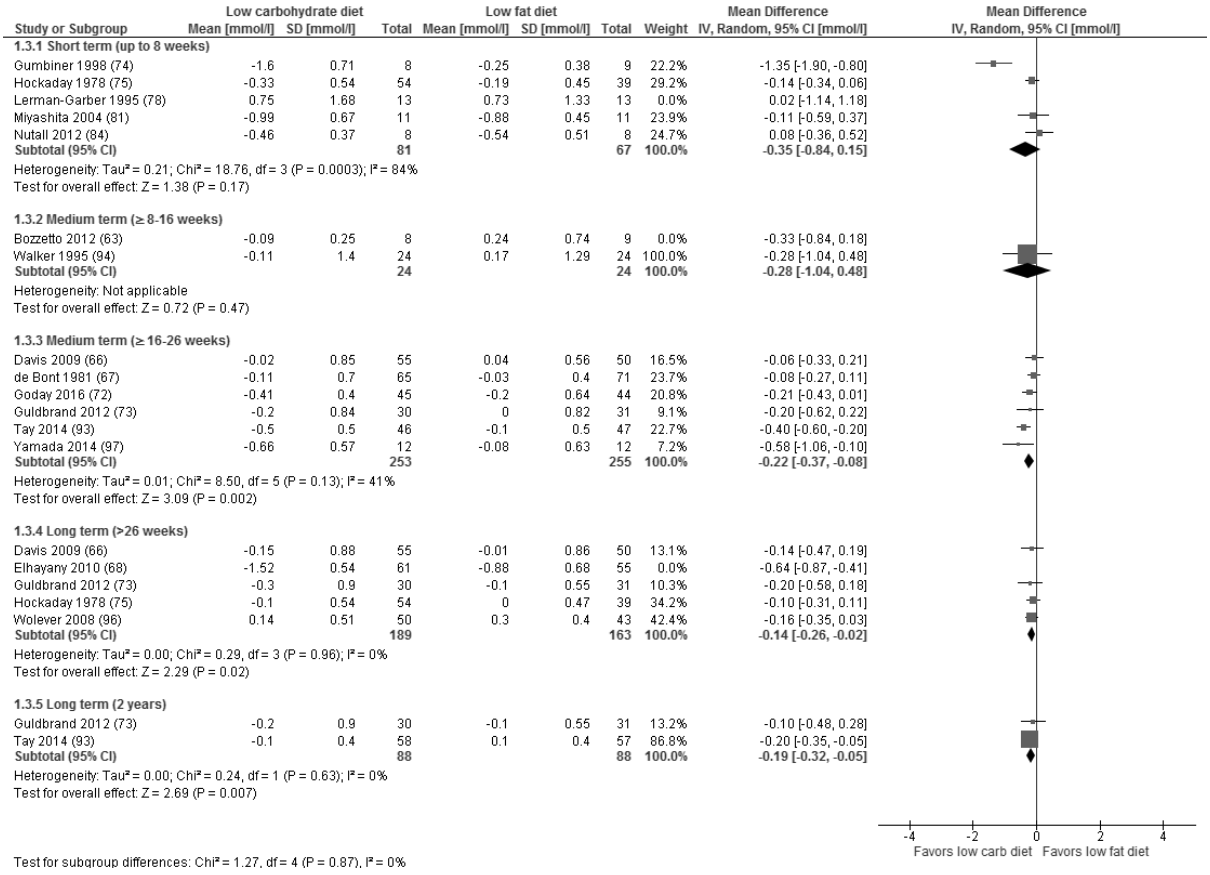


Figure 2d Change from baseline of fasting HDL, without Lerman-Garber 1995 (78) in data and analysis 1.4.1, Bozzetto 2012 (63) in 1.4.2, and Elhayany 2010 (68) in 1.4.4

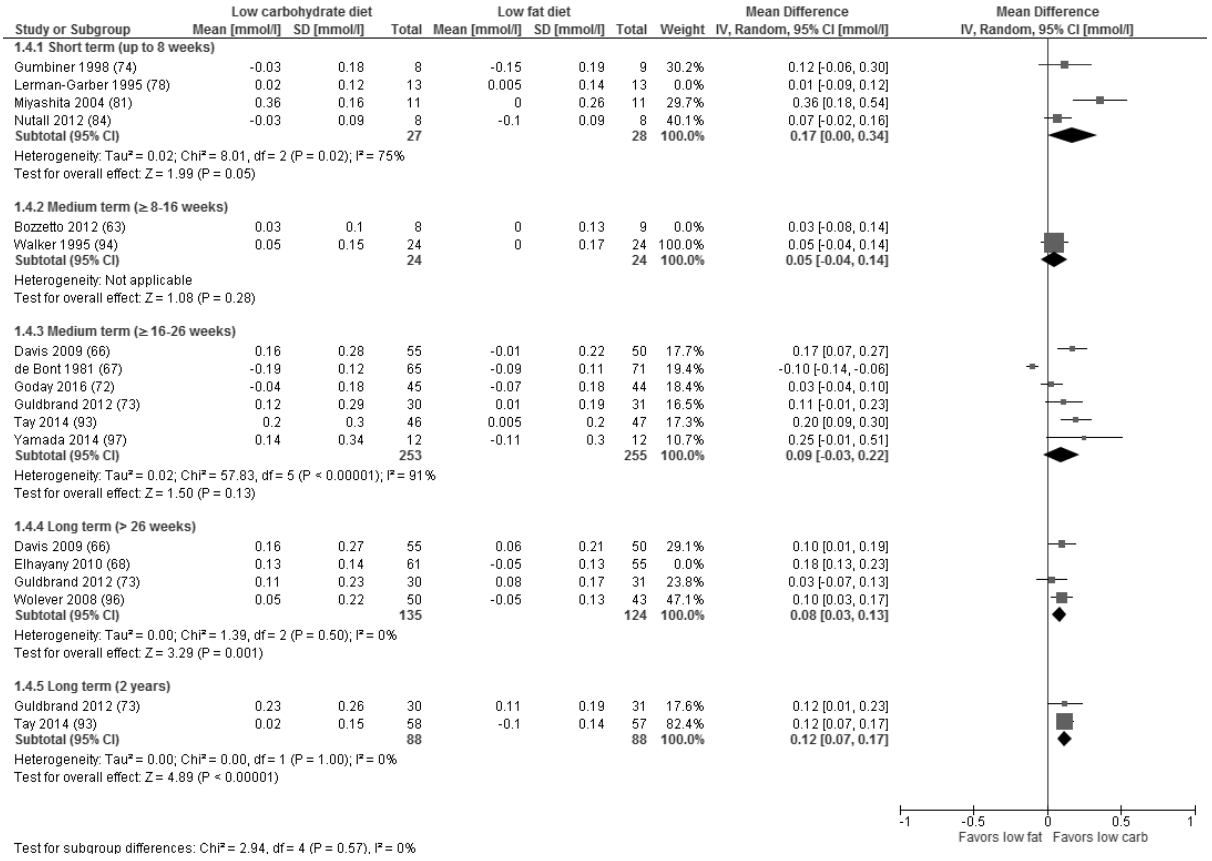


Figure 2e Change from baseline of fasting LDL, without Lerman-Garber 1995 (78) in data and analysis 1.5.1, Bozzetto 2012 (63) in 1.5.2, and Elhayany 2010 (68) in 1.5.4

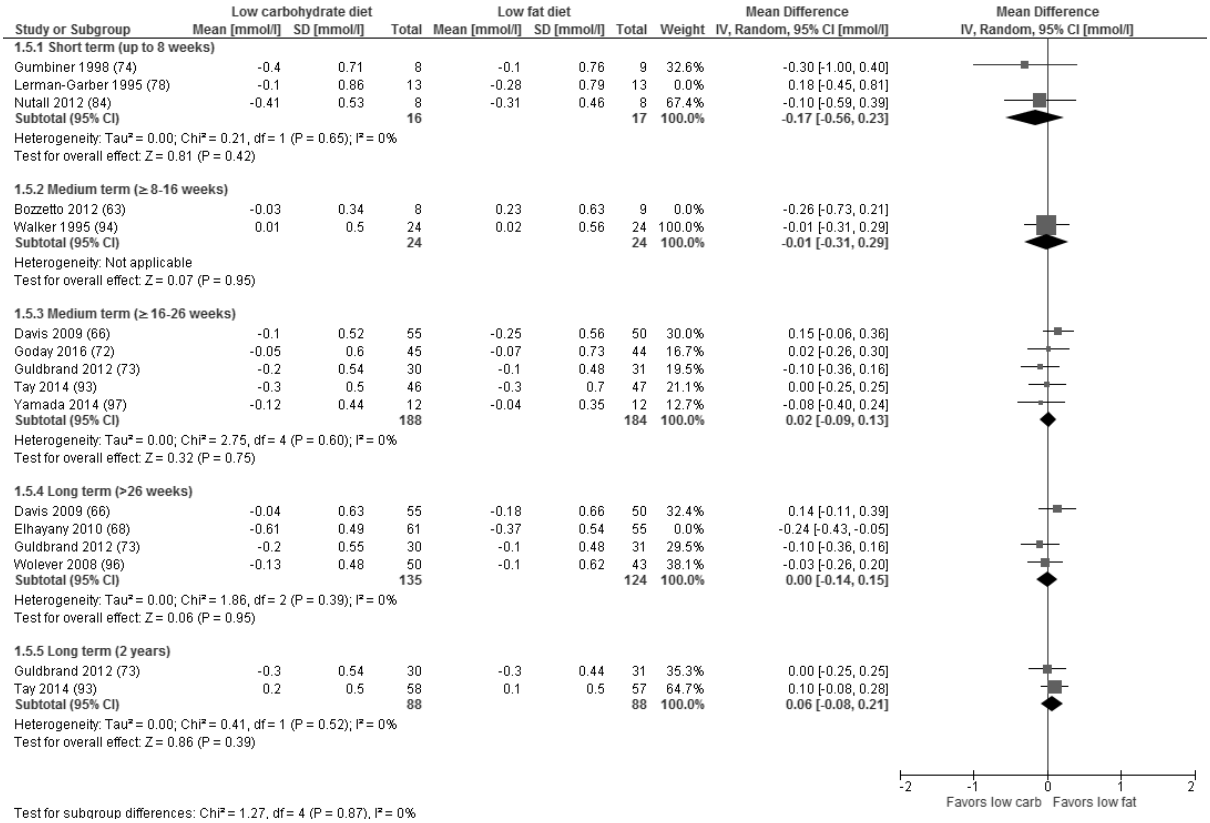


Figure 2f Change from baseline of body weight, without Lerman-Garber 1995 (78) in data and analysis 1.6.1, Bozzetto 2012 (63) in 1.6.2, Elhayany 2010 (68) 1.6.4, and Nielsen 2005 (83) in 1.6.2 and 1.6.3

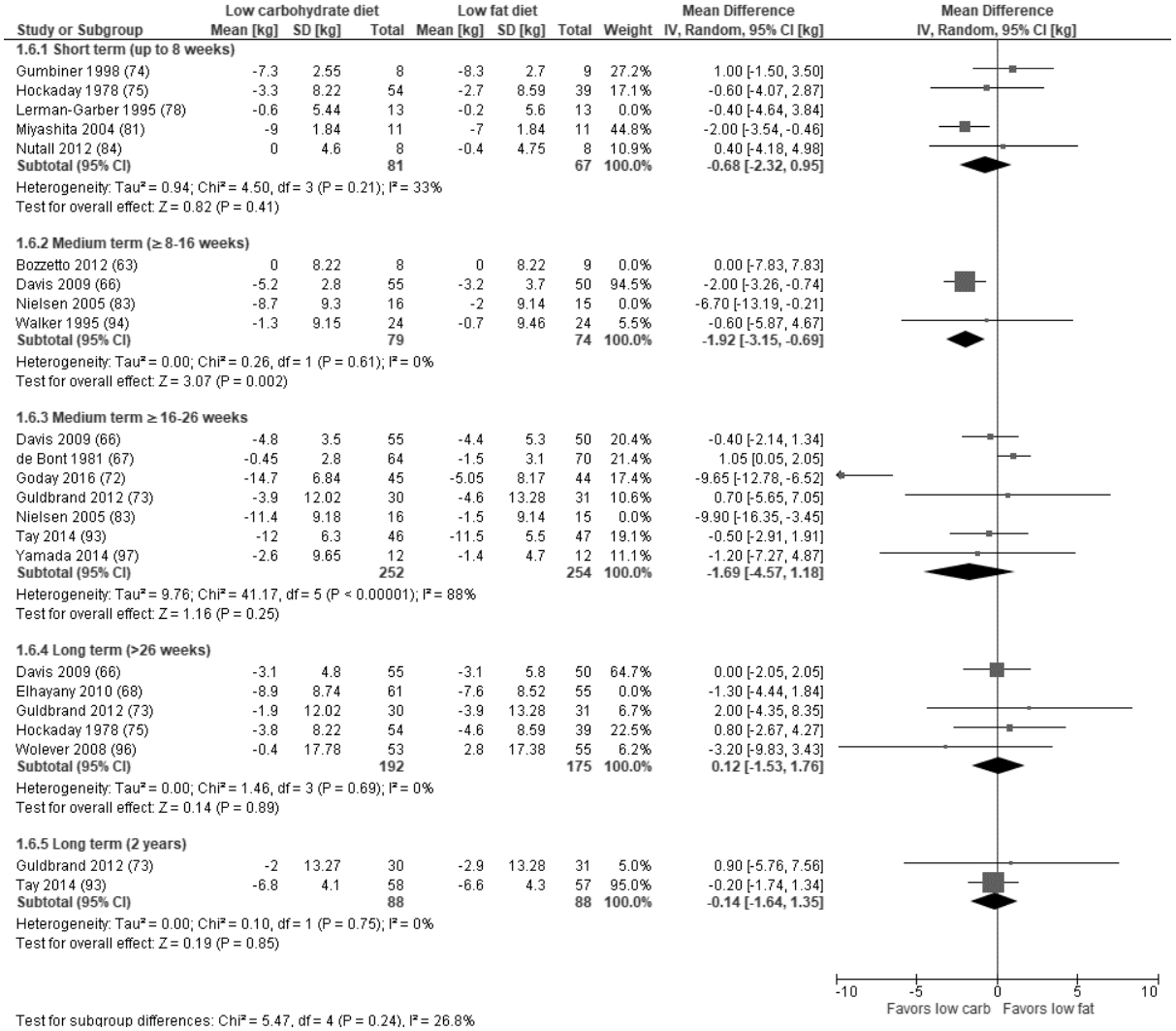


Figure 2g Change from baseline of BMI, without Nielsen 2005 (83) in data and analyses 1.7.1 and 1.7.2 and Elhayani 2010 (68) in 1.7.3

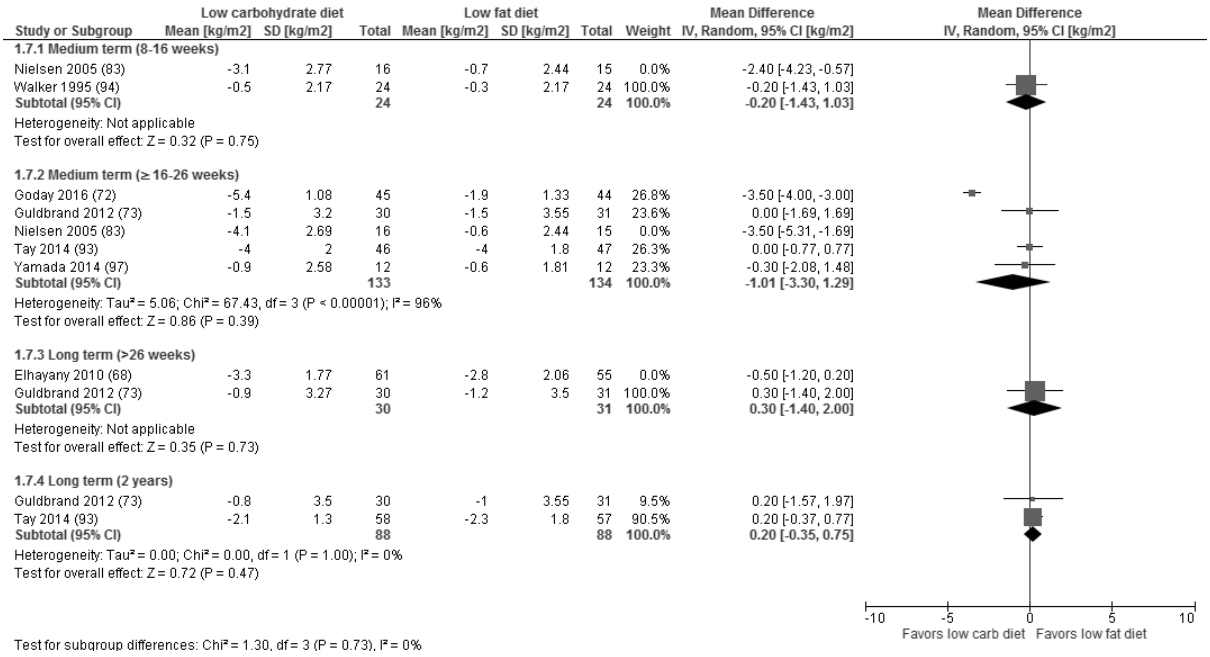
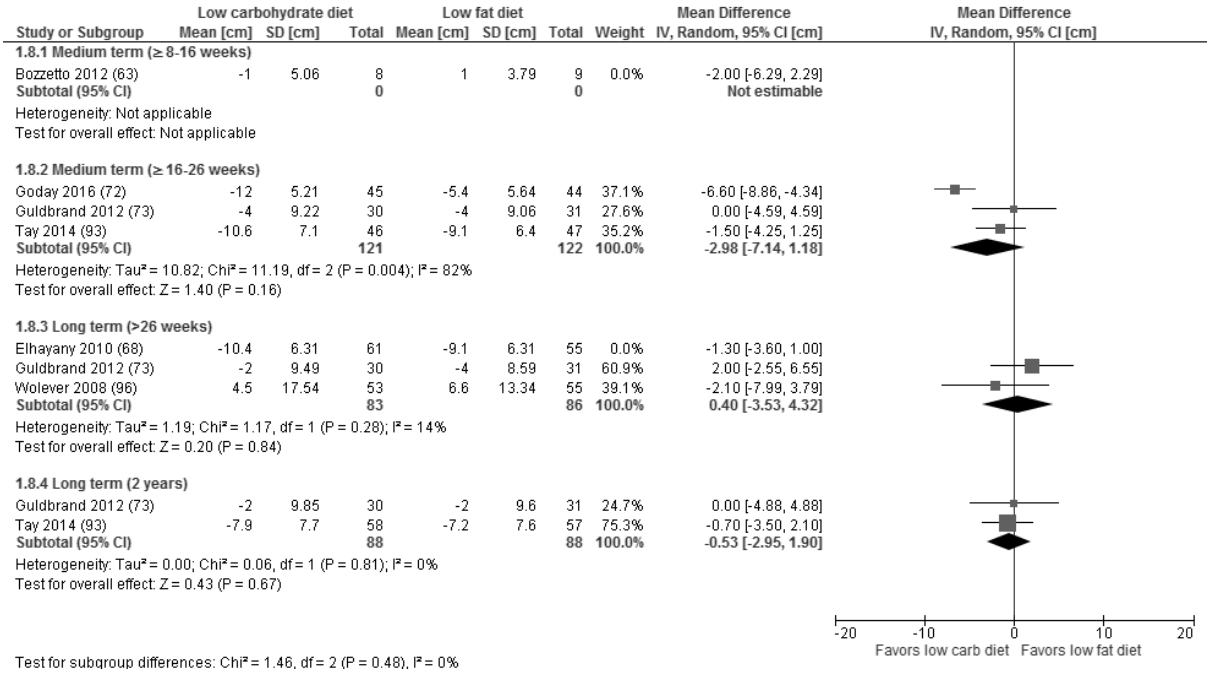


Figure 2h Change from baseline of waist circumference, without Bozzetto 2012 (63) in data and analysis 1.8.1, and Elhayani 2010 (68) in 1.8.3



Change from baseline of systolic blood and diastolic blood pressure , there were no RCTs at high risk of bias or CCTs at serious risk of bias

Supplemental Figure 3 Sensitivity analyses 'Removing studies that cause substantial heterogeneity' (pooled analysis of at least 3 studies)(Figure 3a-3h)

Figure 3a Change from baseline of HbA1c, without Nielsen 2005 (83) in data and analysis 1.1.2, de Bont 1981 (67) in 1.1.3 and Tay 2014 (93) in 1.1.3

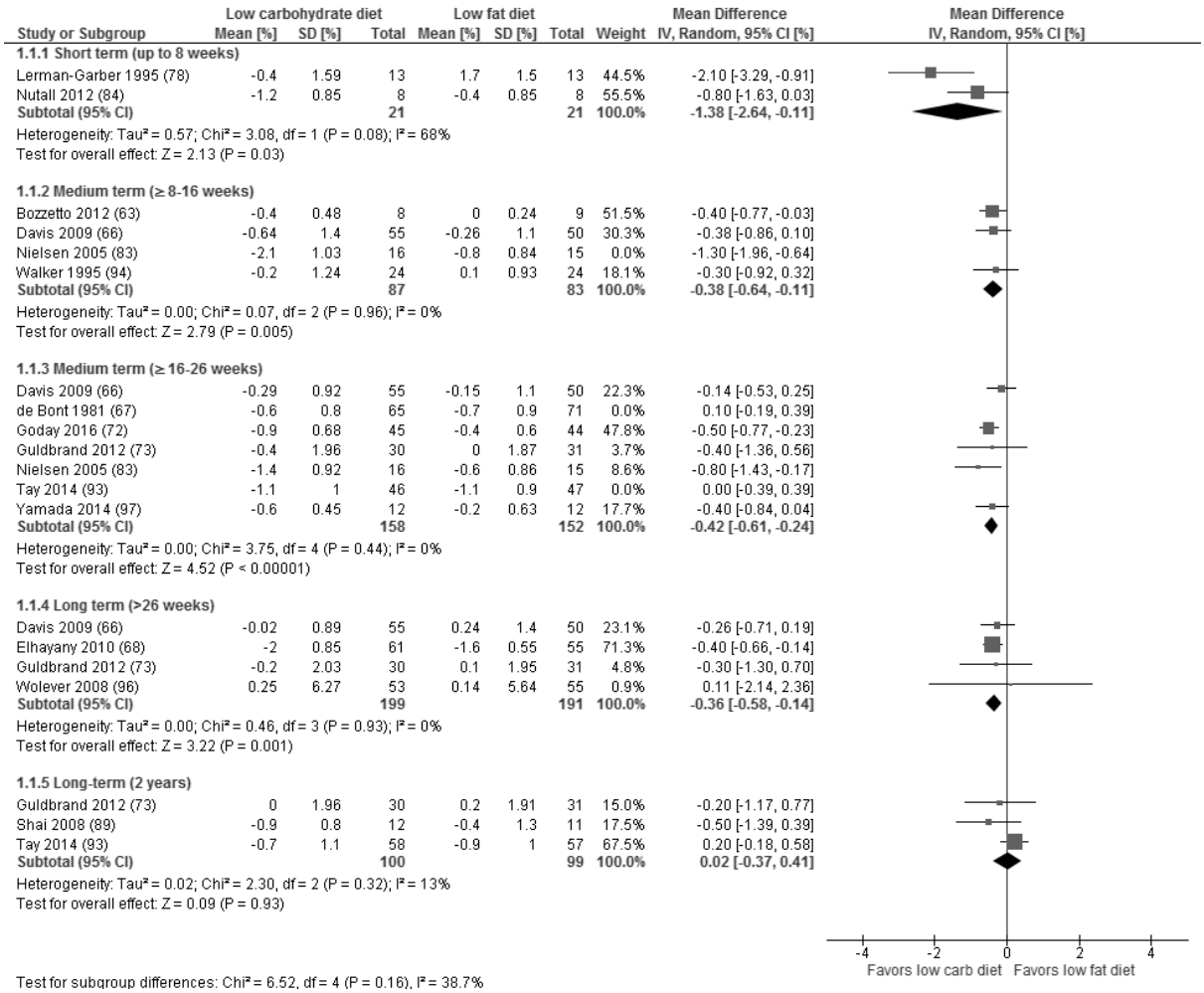


Figure 3b Change from baseline of fasting glucose, without de Bont 1981 (67) in data and analysis 1.2.3, Hockaday 1988 (75) in 1.2.1 and 1.2.4, Tay 2014 (93) in 1.2.3 and Wolever 2008 (96) in 1.2.4

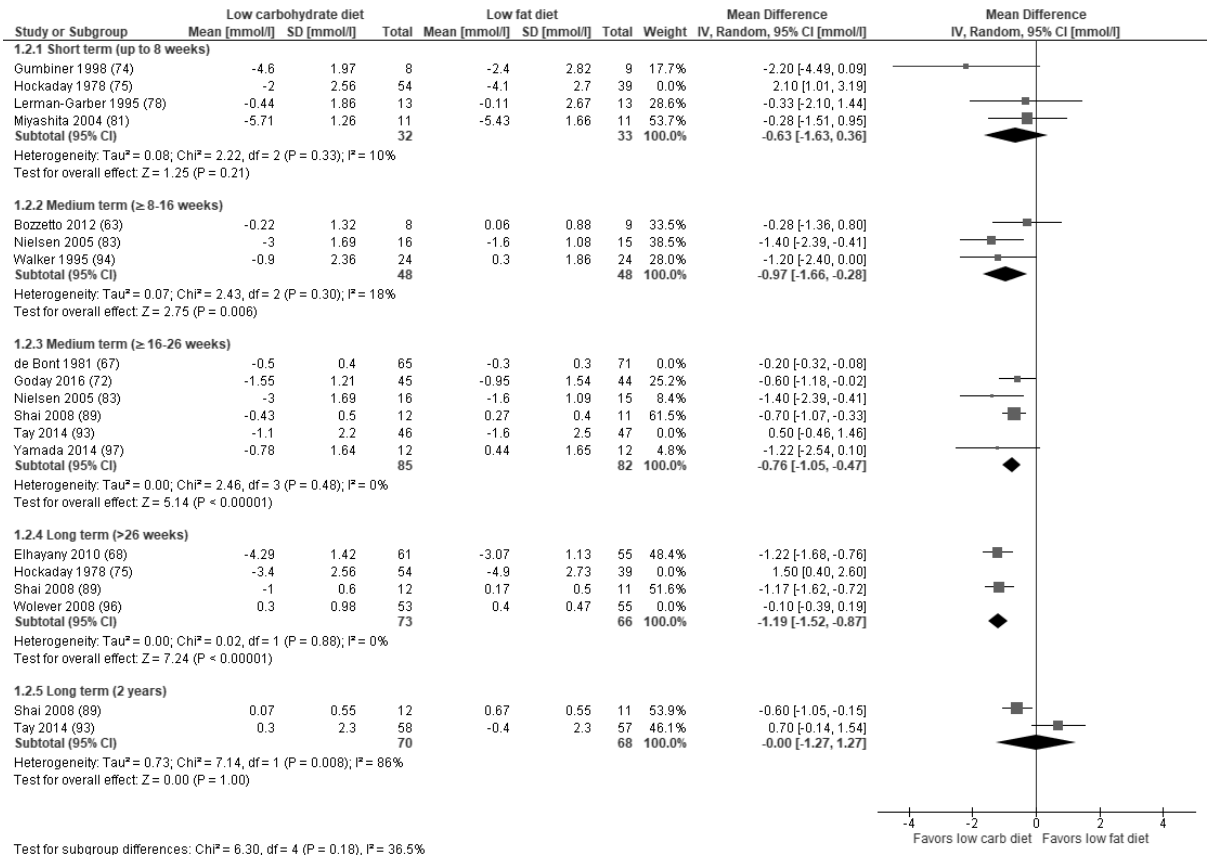


Figure 3c Change from baseline of fasting triglycerides, without Gumbiner 1998 (74) in data and analysis 1.3.1 and Elhayany 2010 (68) in 1.3.4

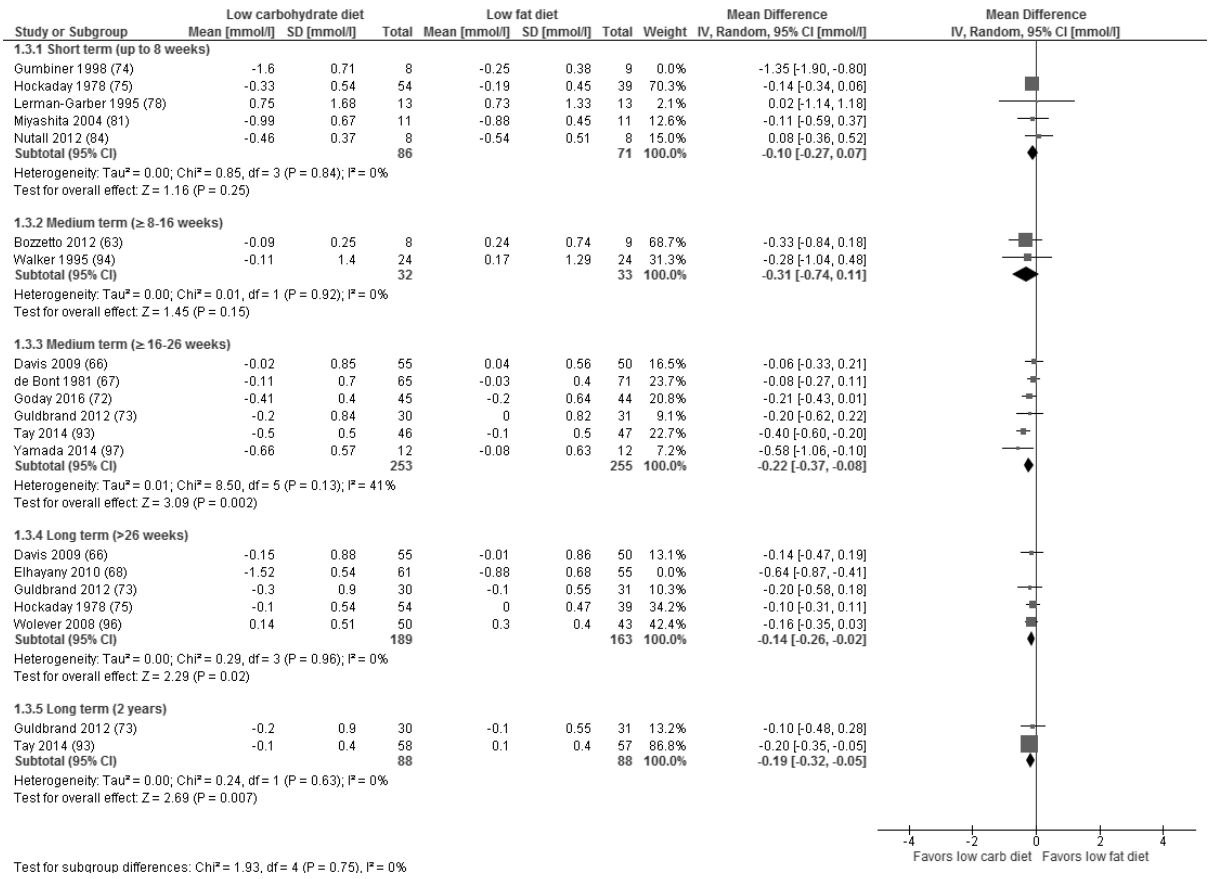


Figure 3d Change from baseline of fasting HDL, without Miyashita 2004 (81) in data and analysis 1.4.1, de Bont 1981 (67) in 1.4.3, Goday 2016 (72) in 1.4.3, Elhayany 2010 (68) in 1.4.4

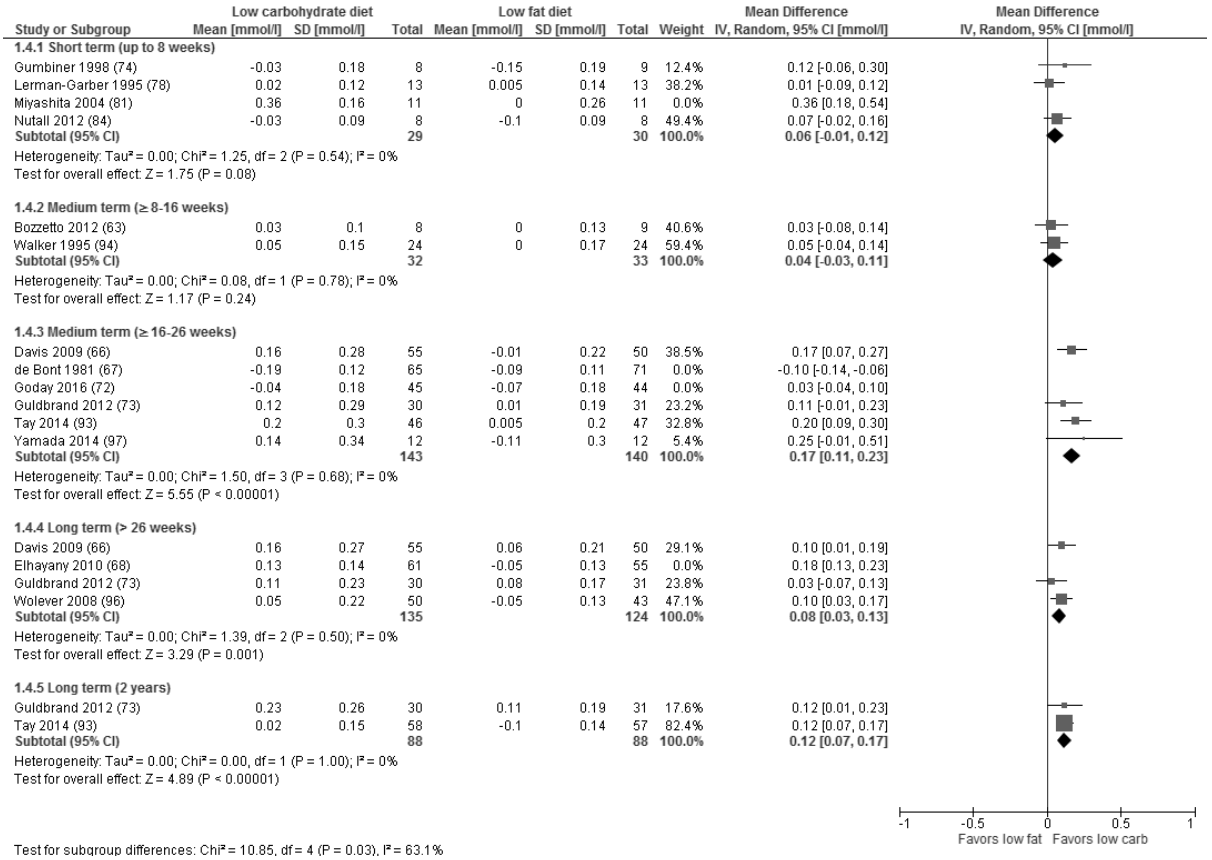


Figure 3e Change from baseline of fasting LDL, without Elhayany 2010 (68) in data and analysis 1.5.4

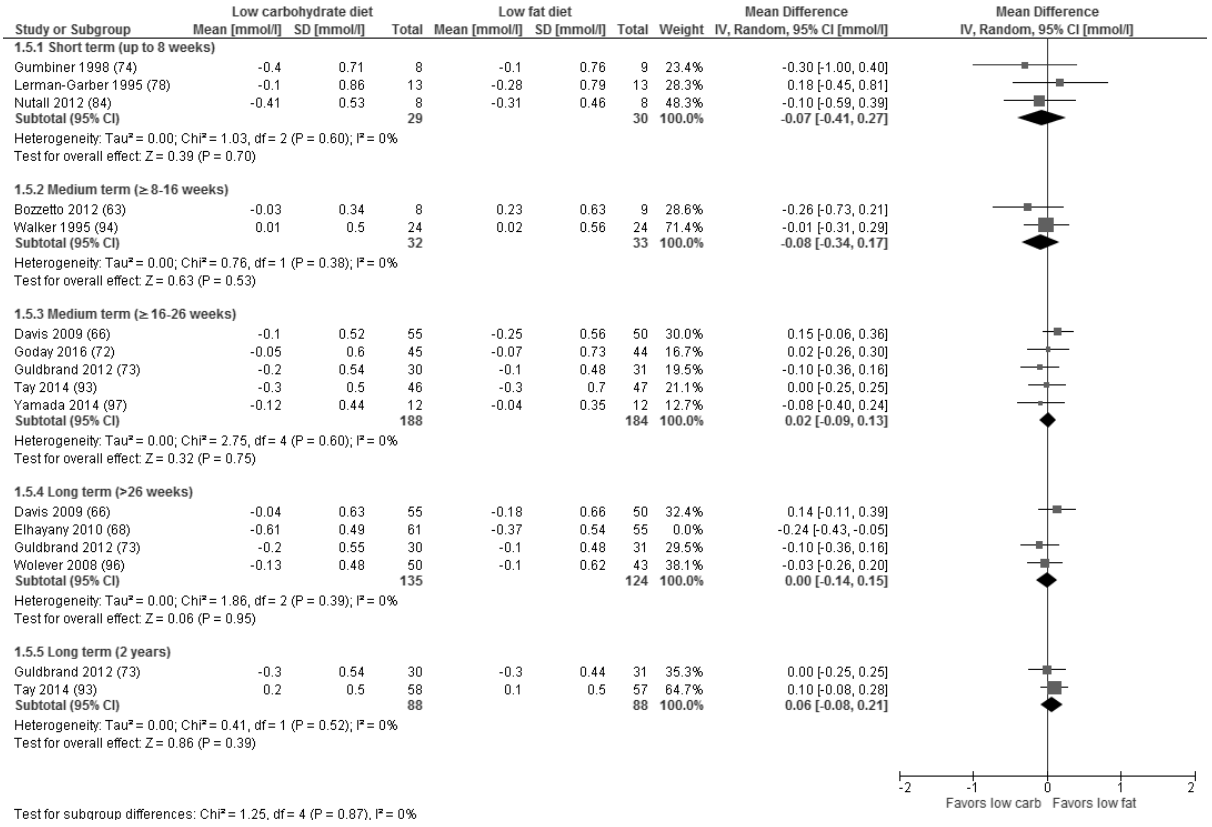


Figure 3f Change from baseline of body weight, without Goday 2016 (72) and Nielsen 2005 (83) both in data and analysis 1.6.3

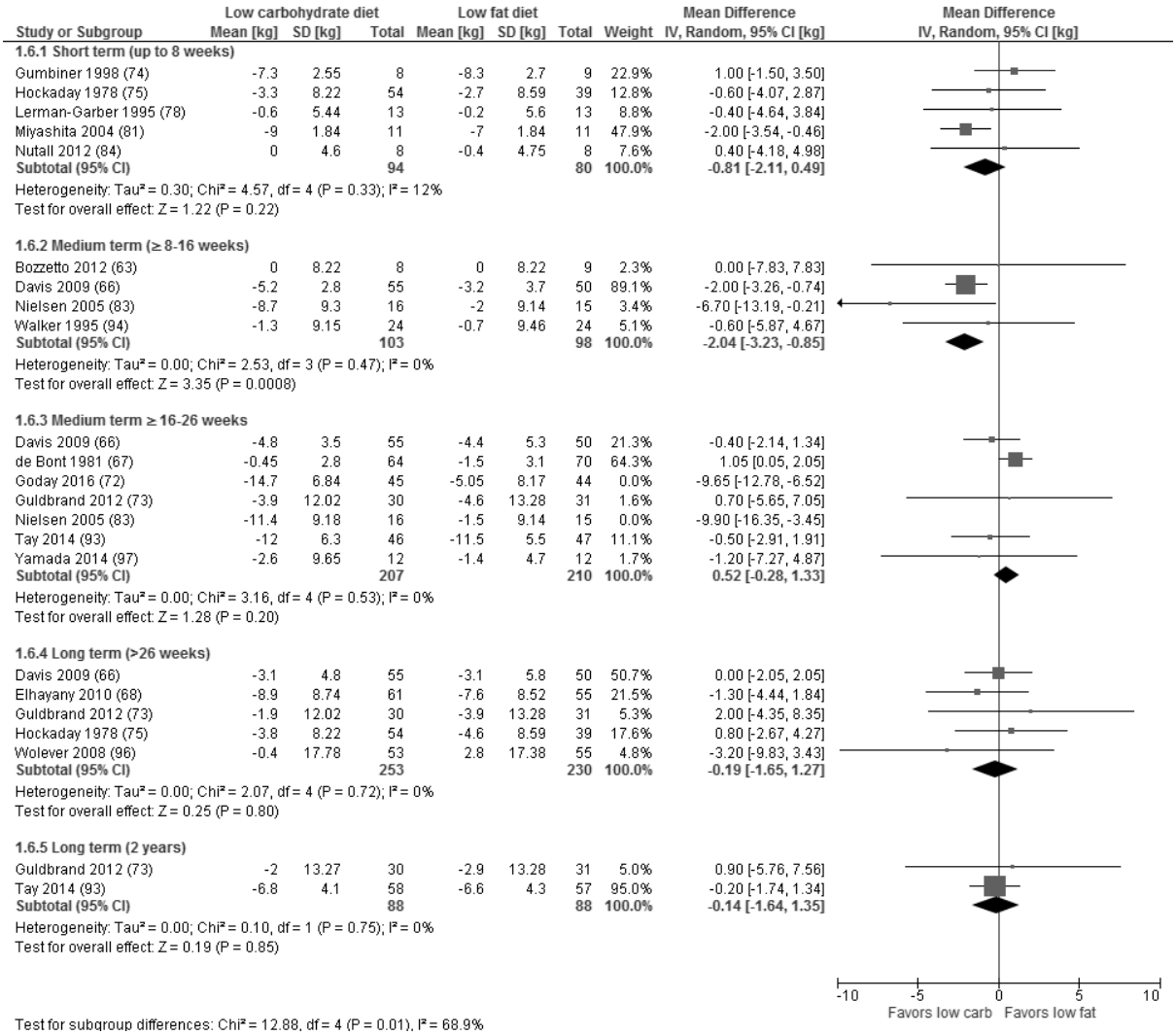


Figure 3g Change from baseline of BMI, without Goday 2016 (72) and Nielsen 2005 (83) both in data and analysis 1.7.2

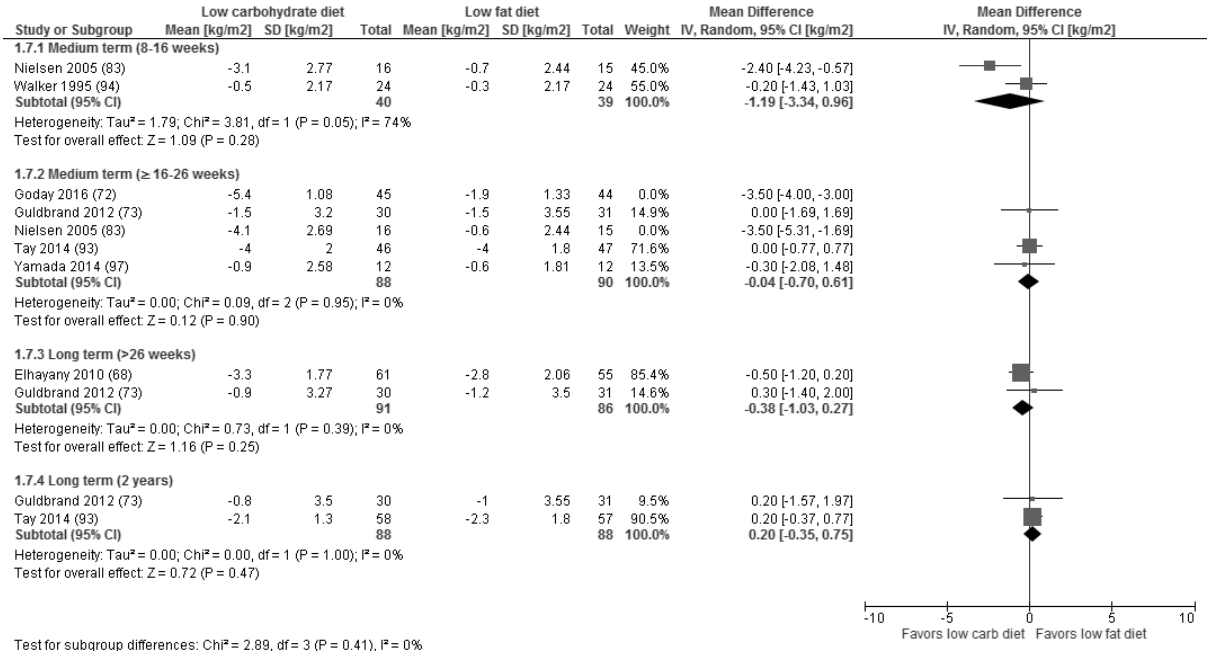
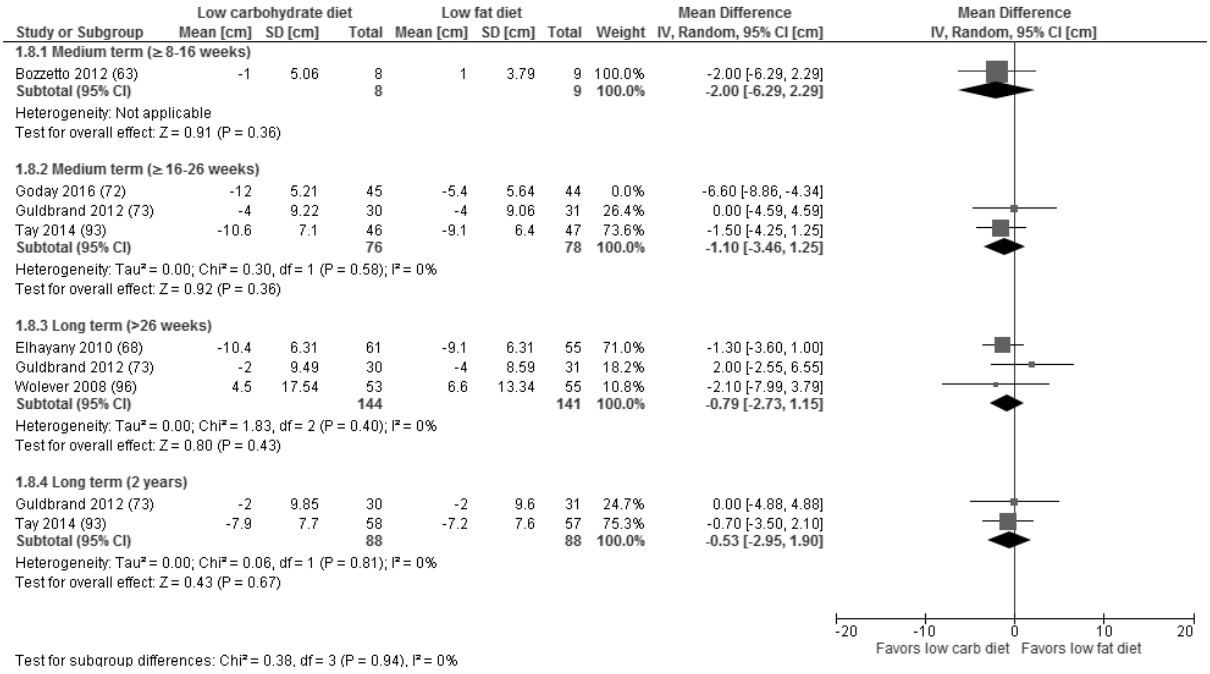
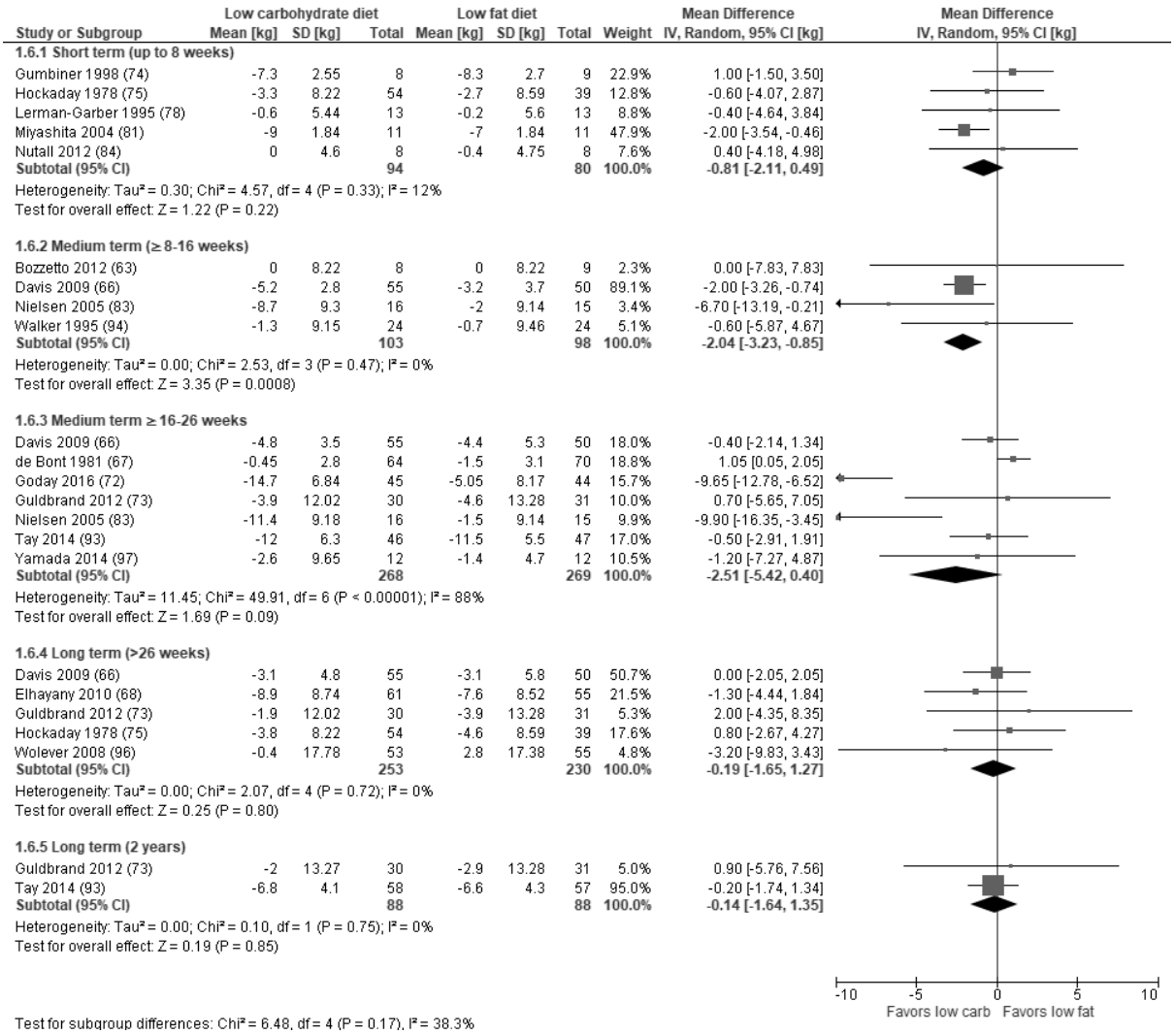


Figure 3h Change from baseline of waist circumference, without Goday 2016 (72) in data and analysis 1.8.2

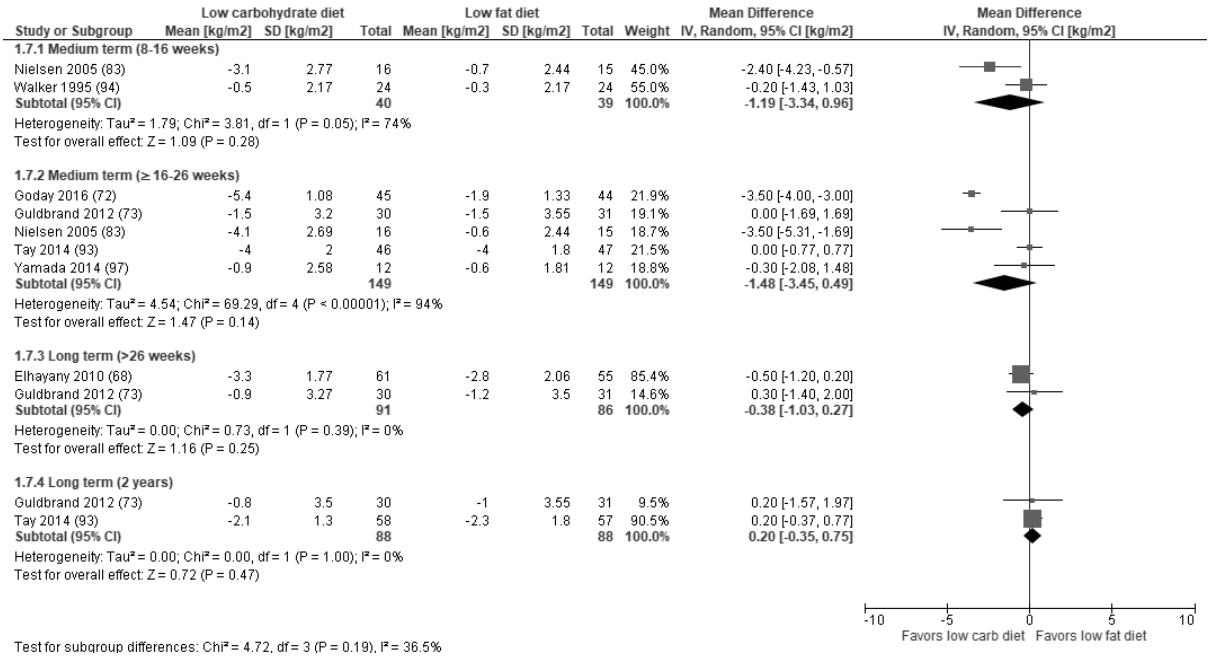


Change from baseline of systolic and diastolic blood pressure not applicable

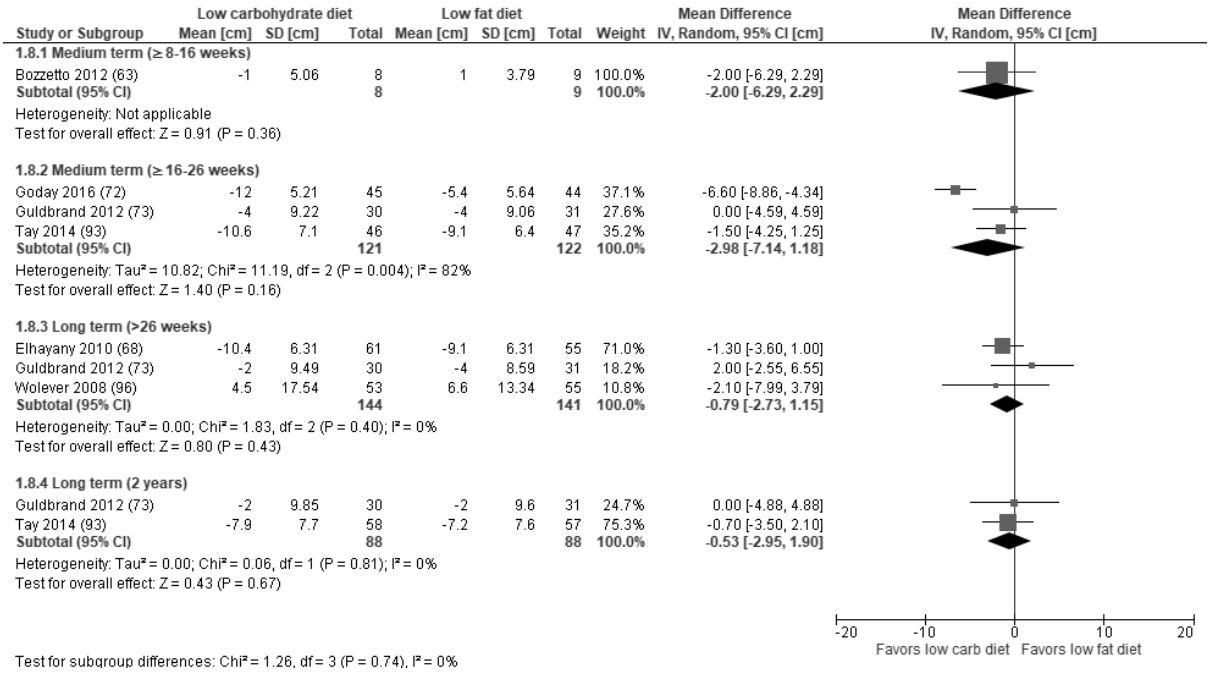
Supplemental Figure 4 Change from baseline of bodyweight



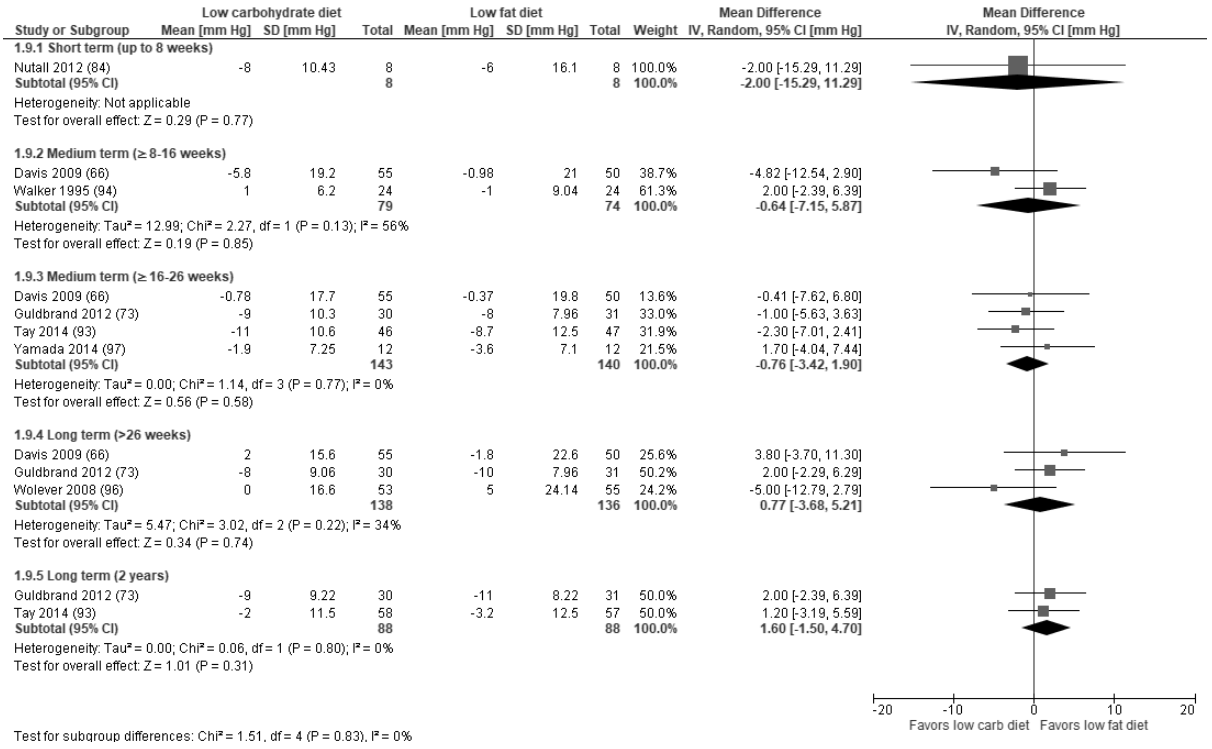
Supplemental Figure 5 Change from baseline of BMI



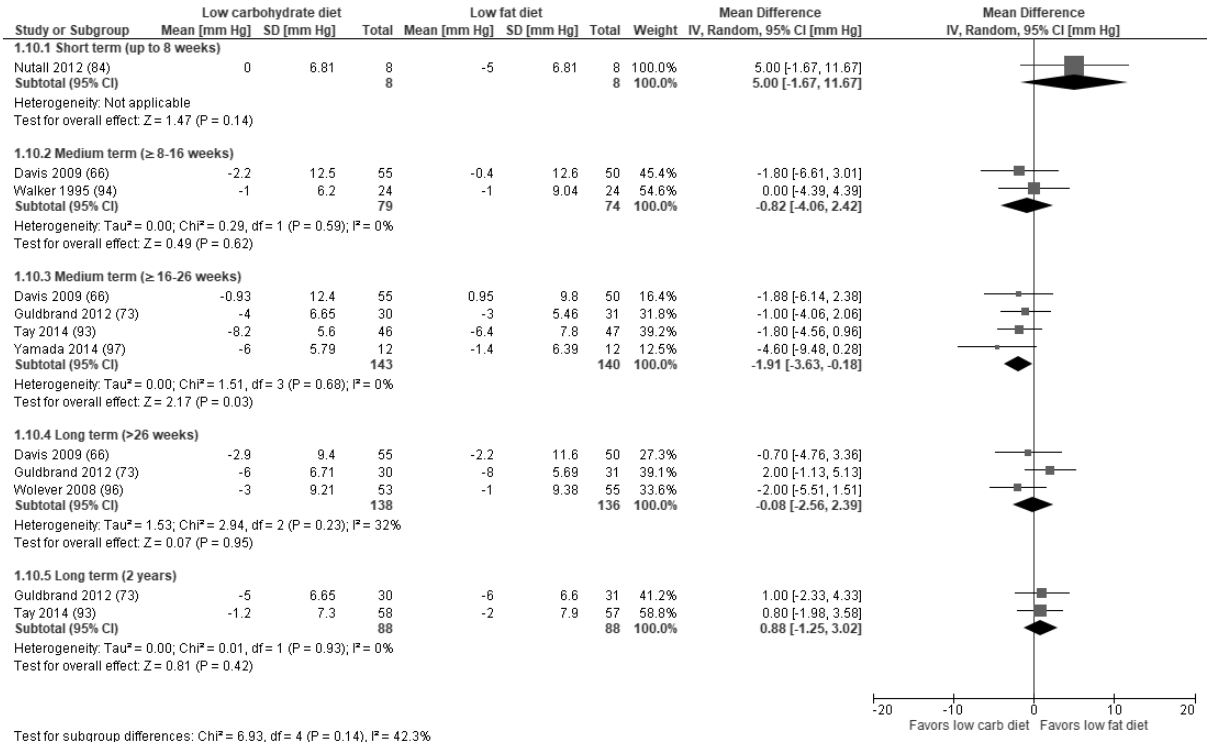
Supplemental Figure 6 Change from baseline of waist circumference



Supplemental Figure 7 Change from baseline of systolic blood pressure



Supplemental Figure 8 Change from baseline of diastolic blood pressure



Supplemental Table 1 Literature search strategy for all the databases

Search strategy for PubMed
((("Diabetes Mellitus, Type 2"[Mesh] OR "type 2 diabetes"[tw] OR "Ketosis-Resistant Diabetes"[tw] OR "Non-Insulin-Dependent Diabetes"[tw] OR "Stable Diabetes"[tw] OR "NIDDM"[tw] OR "Type 2 Diabetes"[tw] OR "Noninsulin-Dependent Diabetes"[tw] OR "Noninsulin Dependent Diabetes"[tw] OR "Type II Diabetes"[tw] OR "Type Two Diabetes"[tw] OR "Adult-Onset Diabetes"[tw] OR "Non-Insulin-Dependent Dm"[tw] OR "Stable Dm"[tw] OR "Type 2 Dm"[tw] OR "Noninsulin-Dependent Dm"[tw] OR "Noninsulin Dependent Dm"[tw] OR "Type II Dm"[tw] OR "Adult-Onset Dm"[tw] OR "Non-Insulin-Dependent Diabetic"[tw] OR "Type 2 Diabetic"[tw] OR "Noninsulin-Dependent Diabetic"[tw] OR "Noninsulin Dependent Diabetic"[tw] OR "Type II Diabetic"[tw] OR "Type Two Diabetic"[tw] OR "Adult-Onset Diabetic"[tw] OR "Type 2 Diabetics"[tw] OR "Noninsulin-Dependent Diabetics"[tw] OR "Noninsulin Dependent Diabetics"[tw] OR "Type II Diabetics"[tw] OR "Type Two Diabetics"[tw] OR "Adult-Onset Diabetics"[tw] OR "diabetes type 2"[tw] OR "diabetes type ii"[tw] OR "diabetes mellitus type 2"[tw] OR "diabetes mellitus type ii"[tw] OR "dm type 2"[tw] OR "dm type ii"[tw] OR "T2D"[tw] OR (("type 2"[tw] OR "type2"[tw] OR "type two"[tw] OR "type ii"[tw] OR "typeii"[tw]) AND (diabete*[tw] OR diabetic*[tw] OR diabet*[tw])) OR ("diabetes"[tw] AND (("Randomized Controlled Trial"[ptyp] OR "RCT"[tw] OR random*[tw] OR "Comparative Study"[ptyp] OR "Clinical Trial"[ptyp])))) AND ("Diet, Carbohydrate-Restricted"[Mesh] OR "Carbohydrate-Restricted"[tw] OR "Carbohydrate Restricted"[tw] OR "Carbohydrates-Restricted"[tw] OR "Carbohydrates Restricted"[tw] OR Carbohydrate Restrict*[tw] OR Carbohydrates Restrict*[tw] OR "carbohydrate free"[tw] OR "carbohydrates free"[tw] OR carbohydrate free*[tw] OR carbohydrates free*[tw] OR "Low Carbohydrate"[tw] OR "Low Carbohydrates"[tw] OR Low Carbohydrat*[tw] OR "South Beach Diet"[tw] OR "South Beach Diets"[tw] OR "Atkins Diet"[tw] OR Atkins Diet*[tw] OR low carb*[tw]) AND ("Diet, Fat-Restricted"[Mesh] OR "low fat"[tw] OR low fat*[tw] OR "Fat-Restricted"[tw] OR "Fat Restricted"[tw] OR "Fats-Restricted"[tw] OR "Fats Restricted"[tw] OR Fat-Restrict*[tw] OR Fat Restrict*[tw] OR "Low-Fat"[tw] OR "Low Fat"[tw] OR Low-Fat*[tw] OR Low Fat*[tw] OR "Fat-Free"[tw] OR "Fat Free"[tw] OR "Fats-Free"[tw] OR "Fats Free"[tw] OR Fat-Free*[tw] OR Fat Free*[tw] OR Fats-Free*[tw] OR Fats Free*[tw])) **OR** (("Diabetes Mellitus, Type 2"[majr] OR "type 2 diabetes"[ti] OR "Ketosis-Resistant Diabetes"[ti] OR "Non-Insulin-Dependent Diabetes"[ti] OR "Stable Diabetes"[ti] OR "NIDDM"[ti] OR "Type 2 Diabetes"[ti] OR "Noninsulin-Dependent Diabetes"[ti] OR "Noninsulin Dependent Diabetes"[ti] OR "Type II Diabetes"[ti] OR "Type Two Diabetes"[ti] OR "Adult-Onset Diabetes"[ti] OR "Non-Insulin-Dependent Dm"[ti] OR "Stable Dm"[ti] OR "Type 2 Dm"[ti] OR "Noninsulin-Dependent Dm"[ti] OR "Noninsulin Dependent Dm"[ti] OR "Type II Dm"[ti] OR "Adult-Onset Dm"[ti] OR "Non-Insulin-Dependent Diabetic"[ti] OR "Type 2 Diabetic"[ti] OR "Noninsulin-Dependent Diabetic"[ti] OR "Noninsulin Dependent Diabetic"[ti] OR "Type II Diabetic"[ti] OR "Type Two Diabetic"[ti] OR "Adult-Onset Diabetic"[ti] OR "Type 2 Diabetics"[ti] OR "Noninsulin-Dependent Diabetics"[ti] OR "Noninsulin Dependent Diabetics"[ti] OR "Type II Diabetics"[ti] OR "Type Two Diabetics"[ti] OR "Adult-Onset Diabetics"[ti] OR "diabetes type 2"[ti] OR "diabetes type ii"[ti] OR "diabetes mellitus type 2"[ti] OR "diabetes mellitus type ii"[ti] OR "dm type 2"[ti] OR "dm type ii"[ti] OR "T2D"[ti] OR (("type 2"[ti] OR "type2"[ti] OR "type two"[ti] OR "type ii"[ti] OR "typeii"[ti]) AND (diabete*[ti] OR diabetic*[ti] OR diabet*[ti])) OR"diabetes"[ti]) AND ("Diet, Carbohydrate-Restricted"[majr] OR "Carbohydrate-Restricted"[tiab] OR "Carbohydrate Restricted"[tiab] OR "Carbohydrates-Restricted"[tiab] OR "Carbohydrates

Restricted"[tiab] OR Carbohydrate Restrict*[tiab] OR Carbohydrates Restrict*[tiab] OR "carbohydrate free"[tiab] OR "carbohydrates free"[tiab] OR carbohydrate free*[tiab] OR carbohydrates free*[tiab] OR "Low Carbohydrate"[tiab] OR "Low Carbohydrates"[tiab] OR Low Carbohydrat*[tiab] OR "South Beach Diet"[tiab] OR "South Beach Diets"[tiab] OR "Atkins Diet"[tiab] OR Atkins Diet*[tiab] OR low carb*[tiab] OR "Diet, Fat-Restricted"[majr] OR "low fat"[tiab] OR low fat*[tiab] OR "Fat-Restricted"[tiab] OR "Fat Restricted"[tiab] OR "Fats-Restricted"[tiab] OR "Fats Restricted"[tiab] OR Fat-Restrict*[tiab] OR Fat Restrict*[tiab] OR "Low-Fat"[tiab] OR "Low Fat"[tiab] OR Low-Fat*[tiab] OR Low Fat*[tiab] OR "Fat-Free"[tiab] OR "Fat Free"[tiab] OR "Fats-Free"[tiab] OR "Fats Free"[tiab] OR Fat-Free*[tiab] OR Fat Free*[tiab] OR Fats-Free*[tiab] OR Fats Free*[tiab]) AND ("Randomized Controlled Trial"[ptyp] OR "RCT"[tw] OR random*[tw] OR "Clinical Trial"[ptyp]) **OR** (("Diabetes Mellitus, Type 2"[majr] OR "type 2 diabetes"[ti] OR "Ketosis-Resistant Diabetes"[ti] OR "Non-Insulin-Dependent Diabetes"[ti] OR "Stable Diabetes"[ti] OR "NIDDM"[ti] OR "Type 2 Diabetes"[ti] OR "Noninsulin-Dependent Diabetes"[ti] OR "Noninsulin Dependent Diabetes"[ti] OR "Type II Diabetes"[ti] OR "Type Two Diabetes"[ti] OR "Adult-Onset Diabetes"[ti] OR "Non-Insulin-Dependent Dm"[ti] OR "Stable Dm"[ti] OR "Type 2 Dm"[ti] OR "Noninsulin-Dependent Dm"[ti] OR "Noninsulin Dependent Dm"[ti] OR "Type II Dm"[ti] OR "Adult-Onset Dm"[ti] OR "Non-Insulin-Dependent Diabetic"[ti] OR "Type 2 Diabetic"[ti] OR "Noninsulin-Dependent Diabetic"[ti] OR "Noninsulin Dependent Diabetic"[ti] OR "Type II Diabetic"[ti] OR "Type Two Diabetic"[ti] OR "Adult-Onset Diabetic"[ti] OR "Type 2 Diabetics"[ti] OR "Noninsulin-Dependent Diabetics"[ti] OR "Noninsulin Dependent Diabetics"[ti] OR "Type II Diabetics"[ti] OR "Type Two Diabetics"[ti] OR "Adult-Onset Diabetics"[ti] OR "diabetes type 2"[ti] OR "diabetes type ii"[ti] OR "diabetes mellitus type 2"[ti] OR "diabetes mellitus type ii"[ti] OR "dm type 2"[ti] OR "dm type ii"[ti] OR "T2D"[ti] OR (("type 2"[ti] OR "type2"[ti] OR "type two"[ti] OR "type ii"[ti] OR "typeii"[ti]) AND (diabete*[ti] OR diabetic*[ti] OR diabet*[ti]))) AND ("Diet, Carbohydrate Loading"[mesh] OR "Carbohydrate Loading"[tw] OR "Carbohydrate-Rich"[tw] OR "Carbohydrate Rich"[tw] OR "Carbohydrates-Rich"[tw] OR "Carbohydrates Rich"[tw] OR rich carbohydrat*[tw] OR "High Carbohydrate"[tw] OR "High Carbohydrates"[tw] OR High Carbohydrat*[tw] OR high carb*[tw]) AND ("Diet, High-Fat"[Mesh] OR "high fat"[tw] OR high fat*[tw] OR "High-Fat"[tw] OR "High Fat"[tw] OR High-Fat*[tw] OR High Fat*[tw]) AND ("Randomized Controlled Trial"[ptyp] OR "RCT"[tw] OR random*[tw] OR "Clinical Trial"[ptyp])))

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(((exp "Diabetes Mellitus, Type 2"/ OR "type 2 diabetes".mp OR "Ketosis-Resistant Diabetes".mp OR "Non-Insulin-Dependent Diabetes".mp OR "Stable Diabetes".mp OR "NIDDM".mp OR "Type 2 Diabetes".mp OR "Noninsulin-Dependent Diabetes".mp OR "Noninsulin Dependent Diabetes".mp OR "Type II Diabetes".mp OR "Type Two Diabetes".mp OR "Adult-Onset Diabetes".mp OR "Non-Insulin-Dependent Dm".mp OR "Stable Dm".mp OR "Type 2 Dm".mp OR "Noninsulin-Dependent Dm".mp OR "Noninsulin Dependent Dm".mp OR "Type II Dm".mp OR "Adult-Onset Dm".mp OR "Non-Insulin-Dependent Diabetic".mp OR "Type 2 Diabetic".mp OR "Noninsulin-Dependent Diabetic".mp OR "Noninsulin Dependent Diabetic".mp OR "Type II Diabetic".mp OR "Type Two Diabetic".mp OR "Adult-Onset Diabetic".mp OR "Type 2 Diabetics".mp OR "Noninsulin-Dependent Diabetics".mp OR "Noninsulin Dependent Diabetics".mp OR "Type II Diabetics".mp OR "Type Two Diabetics".mp OR "Adult-Onset Diabetics".mp OR "diabetes type 2".mp OR "diabetes type ii".mp OR "diabetes mellitus type 2".mp OR "diabetes mellitus type ii".mp OR "dm type 2".mp OR "dm type ii".mp OR "T2D".mp OR (("type 2".mp OR "type2".mp OR "type two".mp OR "type ii".mp OR

"typeii".mp) AND (diabete*.mp OR diabetic*.mp OR diabet*.mp))) AND (exp "Diet, Carbohydrate-Restricted"/ OR "Carbohydrate-Restricted".mp OR "Carbohydrate Restricted".mp OR "Carbohydrates-Restricted".mp OR "Carbohydrates Restricted".mp OR Carbohydrate Restrict*.mp OR Carbohydrates Restrict*.mp OR "carbohydrate free".mp OR "carbohydrates free".mp OR carbohydrate free*.mp OR carbohydrates free*.mp OR "Low Carbohydrate".mp OR "Low Carbohydrates".mp OR Low Carbohydrat*.mp OR "South Beach Diet".mp OR "South Beach Diets".mp OR "Atkins Diet".mp OR Atkins Diet*.mp OR low carb*.mp) AND (exp "Diet, Fat-Restricted"/ OR "low fat".mp OR low fat*.mp OR "Fat-Restricted".mp OR "Fat Restricted".mp OR "Fats-Restricted".mp OR "Fats Restricted".mp OR Fat-Restrict*.mp OR Fat Restrict*.mp OR "Low-Fat".mp OR "Low Fat".mp OR Low-Fat*.mp OR Low Fat*.mp OR "Fat-Free".mp OR "Fat Free".mp OR "Fats-Free".mp OR "Fats Free".mp OR Fat-Free*.mp OR Fat Free*.mp OR Fats-Free*.mp OR Fats Free*.mp)) **OR** ((exp *"Diabetes Mellitus, Type 2"/ OR "type 2 diabetes".ti OR "Ketosis-Resistant Diabetes".ti OR "Non-Insulin-Dependent Diabetes".ti OR "Stable Diabetes".ti OR "NIDDM".ti OR "Type 2 Diabetes".ti OR "Noninsulin-Dependent Diabetes".ti OR "Noninsulin Dependent Diabetes".ti OR "Type II Diabetes".ti OR "Type Two Diabetes".ti OR "Adult-Onset Diabetes".ti OR "Non-Insulin-Dependent Dm".ti OR "Stable Dm".ti OR "Type 2 Dm".ti OR "Noninsulin-Dependent Dm".ti OR "Noninsulin Dependent Dm".ti OR "Type II Dm".ti OR "Adult-Onset Dm".ti OR "Non-Insulin-Dependent Diabetic".ti OR "Type 2 Diabetic".ti OR "Noninsulin-Dependent Diabetic".ti OR "Noninsulin Dependent Diabetic".ti OR "Type II Diabetic".ti OR "Type Two Diabetic".ti OR "Adult-Onset Diabetic".ti OR "Type 2 Diabetics".ti OR "Noninsulin-Dependent Diabetics".ti OR "Noninsulin Dependent Diabetics".ti OR "Type II Diabetics".ti OR "Type Two Diabetics".ti OR "Adult-Onset Diabetics".ti OR "diabetes type 2".ti OR "diabetes type ii".ti OR "diabetes mellitus type 2".ti OR "diabetes mellitus type ii".ti OR "dm type 2".ti OR "dm type ii".ti OR "T2D".ti OR (("type 2".ti OR "type2".ti OR "type two".ti OR "type ii".ti OR "typeii".ti) AND (diabete*.ti OR diabetic*.ti OR diabet*.ti))) AND (exp "Diet, Carbohydrate-Restricted"/ OR "Carbohydrate-Restricted".mp OR "Carbohydrate Restricted".mp OR "Carbohydrates-Restricted".mp OR "Carbohydrates Restricted".mp OR Carbohydrate Restrict*.mp OR Carbohydrates Restrict*.mp OR "carbohydrate free".mp OR "carbohydrates free".mp OR carbohydrate free*.mp OR carbohydrates free*.mp OR "Low Carbohydrate".mp OR "Low Carbohydrates".mp OR Low Carbohydrat*.mp OR "South Beach Diet".mp OR "South Beach Diets".mp OR "Atkins Diet".mp OR Atkins Diet*.mp OR low carb*.mp OR exp "Diet, Fat-Restricted"/ OR "low fat".mp OR low fat*.mp OR "Fat-Restricted".mp OR "Fat Restricted".mp OR "Fats-Restricted".mp OR "Fats Restricted".mp OR Fat-Restrict*.mp OR Fat Restrict*.mp OR "Low-Fat".mp OR "Low Fat".mp OR Low-Fat*.mp OR Low Fat*.mp OR "Fat-Free".mp OR "Fat Free".mp OR "Fats-Free".mp OR "Fats Free".mp OR Fat-Free*.mp OR Fat Free*.mp OR Fats-Free*.mp OR Fats Free*.mp) AND ("Randomized Controlled Trial"/ OR "RCT".mp OR random*.mp OR exp "Clinical Trial"/)) **OR** ((exp *"Diabetes Mellitus, Type 2"/ OR "type 2 diabetes".ti OR "Ketosis-Resistant Diabetes".ti OR "Non-Insulin-Dependent Diabetes".ti OR "Stable Diabetes".ti OR "NIDDM".ti OR "Type 2 Diabetes".ti OR "Noninsulin-Dependent Diabetes".ti OR "Noninsulin Dependent Diabetes".ti OR "Type II Diabetes".ti OR "Type Two Diabetes".ti OR "Adult-Onset Diabetes".ti OR "Non-Insulin-Dependent Dm".ti OR "Stable Dm".ti OR "Type 2 Dm".ti OR "Noninsulin-Dependent Dm".ti OR "Noninsulin Dependent Dm".ti OR "Type II Dm".ti OR "Adult-Onset Dm".ti OR "Non-Insulin-Dependent Diabetic".ti OR "Type 2 Diabetic".ti OR "Noninsulin-Dependent Diabetic".ti OR "Noninsulin Dependent Diabetic".ti OR "Type II Diabetic".ti OR "Type Two Diabetic".ti OR "Adult-Onset Diabetic".ti OR "Type 2 Diabetics".ti OR "Noninsulin-Dependent Diabetics".ti OR "Noninsulin Dependent Diabetics".ti OR "Type II

Diabetics".ti OR "Type Two Diabetics".ti OR "Adult-Onset Diabetics".ti OR "diabetes type 2".ti OR "diabetes type ii".ti OR "diabetes mellitus type 2".ti OR "diabetes mellitus type ii".ti OR "dm type 2".ti OR "dm type ii".ti OR "T2D".ti OR (("type 2".ti OR "type2".ti OR "type two".ti OR "type ii".ti OR "typeii".ti) AND (diabete*.ti OR diabetic*.ti OR diabet*.ti))) AND (exp "Diet, Carbohydrate Loading"/ OR "Carbohydrate Loading".mp OR "Carbohydrate-Rich".mp OR "Carbohydrate Rich".mp OR "Carbohydrates-Rich".mp OR "Carbohydrates Rich".mp OR rich carbohydrat*.mp OR "High Carbohydrate".mp OR "High Carbohydrates".mp OR High Carbohydrat*.mp OR high carb*.mp) AND (exp "Diet, High-Fat"/ OR "high fat".mp OR high fat*.mp OR "High-Fat".mp OR "High Fat".mp OR High-Fat*.mp OR High Fat*.mp) AND (exp "Randomized Controlled Trial"/ OR "RCT".mp OR random*.mp OR exp "Clinical Trial"/)))

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((("non insulin dependent diabetes mellitus"/ OR "type 2 diabetes".mp OR "Ketosis-Resistant Diabetes".mp OR "Non-Insulin-Dependent Diabetes".mp OR "Stable Diabetes".mp OR "NIDDM".mp OR "Type 2 Diabetes".mp OR "Noninsulin-Dependent Diabetes".mp OR "Noninsulin Dependent Diabetes".mp OR "Type II Diabetes".mp OR "Type Two Diabetes".mp OR "Adult-Onset Diabetes".mp OR "Non-Insulin-Dependent Dm".mp OR "Stable Dm".mp OR "Type 2 Dm".mp OR "Noninsulin-Dependent Dm".mp OR "Noninsulin Dependent Dm".mp OR "Type II Dm".mp OR "Adult-Onset Dm".mp OR "Non-Insulin-Dependent Diabetic".mp OR "Type 2 Diabetic".mp OR "Noninsulin-Dependent Diabetic".mp OR "Noninsulin Dependent Diabetic".mp OR "Type II Diabetic".mp OR "Type Two Diabetic".mp OR "Adult-Onset Diabetic".mp OR "Type 2 Diabetics".mp OR "Noninsulin-Dependent Diabetics".mp OR "Noninsulin Dependent Diabetics".mp OR "Type II Diabetics".mp OR "Type Two Diabetics".mp OR "Adult-Onset Diabetics".mp OR "diabetes type 2".mp OR "diabetes type ii".mp OR "diabetes mellitus type 2".mp OR "diabetes mellitus type ii".mp OR "dm type 2".mp OR "dm type ii".mp OR "T2D".mp OR (("type 2".mp OR "type2".mp OR "type two".mp OR "type ii".mp OR "typeii".mp) AND (diabete*.mp OR diabetic*.mp OR diabet*.mp))) AND ("low carbohydrate diet"/ OR "Carbohydrate-Restricted".mp OR "Carbohydrate Restricted".mp OR "Carbohydrates-Restricted".mp OR "Carbohydrates Restricted".mp OR Carbohydrate Restrict*.mp OR Carbohydrates Restrict*.mp OR "carbohydrate free".mp OR "carbohydrates free".mp OR carbohydrate free*.mp OR carbohydrates free*.mp OR "Low Carbohydrate".mp OR "Low Carbohydrates".mp OR Low Carbohydrat*.mp OR "South Beach Diet".mp OR "South Beach Diets".mp OR "Atkins Diet".mp OR Atkins Diet*.mp OR low carb*.mp) AND ("low fat diet"/ OR "low fat".mp OR low fat*.mp OR "Fat-Restricted".mp OR "Fat Restricted".mp OR "Fats-Restricted".mp OR "Fats Restricted".mp OR Fat-Restrict*.mp OR Fat Restrict*.mp OR "Low-Fat".mp OR "Low Fat".mp OR Low-Fat*.mp OR Low Fat*.mp OR "Fat-Free".mp OR "Fat Free".mp OR "Fats-Free".mp OR "Fats Free".mp OR Fat-Free*.mp OR Fat Free*.mp OR Fats-Free*.mp OR Fats Free*.mp)) **OR** ((*"non insulin dependent diabetes mellitus"/ OR "type 2 diabetes".ti OR "Ketosis-Resistant Diabetes".ti OR "Non-Insulin-Dependent Diabetes".ti OR "Stable Diabetes".ti OR "NIDDM".ti OR "Type 2 Diabetes".ti OR "Noninsulin-Dependent Diabetes".ti OR "Noninsulin Dependent Diabetes".ti OR "Type II Diabetes".ti OR "Type Two Diabetes".ti OR "Adult-Onset Diabetes".ti OR "Non-Insulin-Dependent Dm".ti OR "Stable Dm".ti OR "Type 2 Dm".ti OR "Noninsulin-Dependent Dm".ti OR "Noninsulin Dependent Dm".ti OR "Type II Dm".ti OR "Adult-Onset Dm".ti OR "Non-Insulin-Dependent Diabetic".ti OR "Type 2 Diabetic".ti OR "Noninsulin-Dependent Diabetic".ti OR "Noninsulin Dependent Diabetic".ti OR "Type II Diabetic".ti OR "Type Two Diabetic".ti OR "Adult-Onset Diabetic".ti OR "Type 2 Diabetics".ti OR "Noninsulin-Dependent Diabetics".ti OR "Noninsulin Dependent Diabetics".ti OR "Type II Diabetics".ti OR "Type Two

Diabetics".ti OR "Adult-Onset Diabetics".ti OR "diabetes type 2".ti OR "diabetes type ii".ti OR "diabetes mellitus type 2".ti OR "diabetes mellitus type ii".ti OR "dm type 2".ti OR "dm type ii".ti OR "T2D".ti OR (("type 2".ti OR "type2".ti OR "type two".ti OR "type ii".ti OR "typeii".ti) AND (diabete*.ti OR diabetic*.ti OR diabet*.ti))) AND ("low carbohydrate diet"/ OR "Carbohydrate-Restricted".mp OR "Carbohydrate Restricted".mp OR "Carbohydrates-Restricted".mp OR "Carbohydrates Restricted".mp OR Carbohydrate Restrict*.mp OR Carbohydrates Restrict*.mp OR "carbohydrate free".mp OR "carbohydrates free".mp OR carbohydrate free*.mp OR carbohydrates free*.mp OR "Low Carbohydrate".mp OR "Low Carbohydrates".mp OR Low Carbohydrat*.mp OR "South Beach Diet".mp OR "South Beach Diets".mp OR "Atkins Diet".mp OR Atkins Diet*.mp OR low carb*.mp OR "low fat diet"/ OR "low fat".mp OR low fat*.mp OR "Fat-Restricted".mp OR "Fat Restricted".mp OR "Fats-Restricted".mp OR "Fats Restricted".mp OR Fat-Restrict*.mp OR Fat Restrict*.mp OR "Low-Fat".mp OR "Low Fat".mp OR Low-Fat*.mp OR Low Fat*.mp OR "Fat-Free".mp OR "Fat Free".mp OR "Fats-Free".mp OR "Fats Free".mp OR Fat-Free*.mp OR Fat Free*.mp OR Fats-Free*.mp OR Fats Free*.mp) AND (exp "Randomized Controlled Trial"/ OR "RCT".mp OR random*.mp OR exp "Clinical Trial"/)) **OR** ((*"non insulin dependent diabetes mellitus"/ OR "type 2 diabetes".ti OR "Ketosis-Resistant Diabetes".ti OR "Non-Insulin-Dependent Diabetes".ti OR "Stable Diabetes".ti OR "NIDDM".ti OR "Type 2 Diabetes".ti OR "Noninsulin-Dependent Diabetes".ti OR "Noninsulin Dependent Diabetes".ti OR "Type II Diabetes".ti OR "Type Two Diabetes".ti OR "Adult-Onset Diabetes".ti OR "Non-Insulin-Dependent Dm".ti OR "Stable Dm".ti OR "Type 2 Dm".ti OR "Noninsulin-Dependent Dm".ti OR "Noninsulin Dependent Dm".ti OR "Type II Dm".ti OR "Adult-Onset Dm".ti OR "Non-Insulin-Dependent Diabetic".ti OR "Type 2 Diabetic".ti OR "Noninsulin-Dependent Diabetic".ti OR "Noninsulin Dependent Diabetic".ti OR "Type II Diabetic".ti OR "Type Two Diabetic".ti OR "Adult-Onset Diabetic".ti OR "Type 2 Diabetics".ti OR "Noninsulin-Dependent Diabetics".ti OR "Noninsulin Dependent Diabetics".ti OR "Type II Diabetics".ti OR "Type Two Diabetics".ti OR "Adult-Onset Diabetics".ti OR "diabetes type 2".ti OR "diabetes type ii".ti OR "diabetes mellitus type 2".ti OR "diabetes mellitus type ii".ti OR "dm type 2".ti OR "dm type ii".ti OR "T2D".ti OR (("type 2".ti OR "type2".ti OR "type two".ti OR "type ii".ti OR "typeii".ti) AND (diabete*.ti OR diabetic*.ti OR diabet*.ti))) AND (exp "Carbohydrate Diet"/ OR "Carbohydrate Loading".mp OR "Carbohydrate-Rich".mp OR "Carbohydrate Rich".mp OR "Carbohydrates-Rich".mp OR "Carbohydrates Rich".mp OR rich carbohydrat*.mp OR "High Carbohydrate".mp OR "High Carbohydrates".mp OR High Carbohydrat*.mp OR high carb*.mp) AND (exp "Lipid Diet"/ OR "high fat".mp OR high fat*.mp OR "High-Fat".mp OR "High Fat".mp OR High-Fat*.mp OR High Fat*.mp) AND (exp "Randomized Controlled Trial"/ OR "RCT".mp OR random*.mp OR exp "Clinical Trial"/))) NOT conference review.pt
Search strategy for Web of Science
((ts=("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2"

OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))) AND TS=("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*") AND TS=("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*")) **OR** (ti=("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))) AND TI=("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*" OR "low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*") AND ts=("Randomized Controlled Trial" OR "RCT" OR random* OR "Clinical Trial")) **OR** (ti=("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii"

OR "typeii") AND (diabete* OR diabetic* OR diabet*))) AND ts=("Carbohydrate Diet" OR "Carbohydrate Loading" OR "Carbohydrate-Rich" OR "Carbohydrate Rich" OR "Carbohydrates-Rich" OR "Carbohydrates Rich" OR "rich carbohydrat*" OR "High Carbohydrate" OR "High Carbohydrates" OR "High Carbohydrat*" OR "high carb*") AND ts=("Lipid Diet" OR "high fat" OR "high fat*" OR "High-Fat" OR "High Fat" OR "High-Fat*" OR "High Fat*") AND ts=("Randomized Controlled Trial" OR "RCT" OR random* OR "Clinical Trial"))) NOT ti=(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats)

Search strategy for Cochrane Library

((("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))):ti,ab,kw AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*"):ti,ab,kw AND ("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*"):ti,ab,kw) **OR** (("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))):ti AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates

Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*" OR "low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*"):ti) **OR** (("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))):ti AND ("Carbohydrate Diet" OR "Carbohydrate Loading" OR "Carbohydrate-Rich" OR "Carbohydrate Rich" OR "Carbohydrates-Rich" OR "Carbohydrates Rich" OR "rich carbohydrat*" OR "High Carbohydrate" OR "High Carbohydrates" OR "High Carbohydrat*" OR "high carb*"):ti,ab,kw AND ("Lipid Diet" OR "high fat" OR "high fat*" OR "High-Fat" OR "High Fat" OR "High-Fat*" OR "High Fat*"):ti,ab,kw))

Search strategy for CENTRAL

((("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))):ti,ab,kw AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*"):ti,ab,kw AND ("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR

"Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*"):ti,ab,kw) **OR** (("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))):ti AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*" OR "low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*"):ti) **OR** (("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))):ti AND ("Carbohydrate Diet" OR "Carbohydrate Loading" OR "Carbohydrate-Rich" OR "Carbohydrate Rich" OR "Carbohydrates-Rich" OR "Carbohydrates Rich" OR "rich carbohydrat*" OR "High Carbohydrate" OR "High Carbohydrates" OR "High Carbohydrat*" OR "high carb*"):ti,ab,kw AND ("Lipid Diet" OR "high fat" OR "high fat*" OR "High-Fat" OR "High Fat" OR "High-Fat*" OR "High Fat*"):ti,ab,kw))
Search strategy for Emcare (OVID version)
((("non insulin dependent diabetes mellitus"/ OR "type 2 diabetes".mp OR "Ketosis-Resistant Diabetes".mp OR "Non-Insulin-Dependent Diabetes".mp OR "Stable Diabetes".mp OR "NIDDM".mp OR "Type 2 Diabetes".mp OR "Noninsulin-Dependent Diabetes".mp OR "Noninsulin Dependent Diabetes".mp OR "Type II Diabetes".mp OR "Type Two Diabetes".mp OR "Adult-Onset Diabetes".mp OR "Non-Insulin-Dependent

Dm".mp OR "Stable Dm".mp OR "Type 2 Dm".mp OR "Noninsulin-Dependent Dm".mp OR "Noninsulin Dependent Dm".mp OR "Type II Dm".mp OR "Adult-Onset Dm".mp OR "Non-Insulin-Dependent Diabetic".mp OR "Type 2 Diabetic".mp OR "Noninsulin-Dependent Diabetic".mp OR "Noninsulin Dependent Diabetic".mp OR "Type II Diabetic".mp OR "Type Two Diabetic".mp OR "Adult-Onset Diabetic".mp OR "Type 2 Diabetics".mp OR "Noninsulin-Dependent Diabetics".mp OR "Noninsulin Dependent Diabetics".mp OR "Type II Diabetics".mp OR "Type Two Diabetics".mp OR "Adult-Onset Diabetics".mp OR "diabetes type 2".mp OR "diabetes type ii".mp OR "diabetes mellitus type 2".mp OR "diabetes mellitus type ii".mp OR "dm type 2".mp OR "dm type ii".mp OR "T2D".mp OR (("type 2".mp OR "type2".mp OR "type two".mp OR "type ii".mp OR "typeii".mp) AND (diabete*.mp OR diabetic*.mp OR diabet*.mp))) AND ("low carbohydrate diet"/ OR "Carbohydrate-Restricted".mp OR "Carbohydrate Restricted".mp OR "Carbohydrates-Restricted".mp OR "Carbohydrates Restricted".mp OR Carbohydrate Restrict*.mp OR Carbohydrates Restrict*.mp OR "carbohydrate free".mp OR "carbohydrates free".mp OR carbohydrate free*.mp OR carbohydrates free*.mp OR "Low Carbohydrate".mp OR "Low Carbohydrates".mp OR Low Carbohydrat*.mp OR "South Beach Diet".mp OR "South Beach Diets".mp OR "Atkins Diet".mp OR Atkins Diet*.mp OR low carb*.mp) AND ("low fat diet"/ OR "low fat".mp OR low fat*.mp OR "Fat-Restricted".mp OR "Fat Restricted".mp OR "Fats-Restricted".mp OR "Fats Restricted".mp OR Fat-Restrict*.mp OR Fat Restrict*.mp OR "Low-Fat".mp OR "Low Fat".mp OR Low-Fat*.mp OR Low Fat*.mp OR "Fat-Free".mp OR "Fat Free".mp OR "Fats-Free".mp OR "Fats Free".mp OR Fat-Free*.mp OR Fat Free*.mp OR Fats-Free*.mp OR Fats Free*.mp)) **OR** ((*"non insulin dependent diabetes mellitus"/ OR "type 2 diabetes".ti OR "Ketosis-Resistant Diabetes".ti OR "Non-Insulin-Dependent Diabetes".ti OR "Stable Diabetes".ti OR "NIDDM".ti OR "Type 2 Diabetes".ti OR "Noninsulin-Dependent Diabetes".ti OR "Noninsulin Dependent Diabetes".ti OR "Type II Diabetes".ti OR "Type Two Diabetes".ti OR "Adult-Onset Diabetes".ti OR "Non-Insulin-Dependent Dm".ti OR "Stable Dm".ti OR "Type 2 Dm".ti OR "Noninsulin-Dependent Dm".ti OR "Noninsulin Dependent Dm".ti OR "Type II Dm".ti OR "Adult-Onset Dm".ti OR "Non-Insulin-Dependent Diabetic".ti OR "Type 2 Diabetic".ti OR "Noninsulin-Dependent Diabetic".ti OR "Noninsulin Dependent Diabetic".ti OR "Type II Diabetic".ti OR "Type Two Diabetic".ti OR "Adult-Onset Diabetic".ti OR "Type 2 Diabetics".ti OR "Noninsulin-Dependent Diabetics".ti OR "Noninsulin Dependent Diabetics".ti OR "Type II Diabetics".ti OR "Type Two Diabetics".ti OR "Adult-Onset Diabetics".ti OR "diabetes type 2".ti OR "diabetes type ii".ti OR "diabetes mellitus type 2".ti OR "diabetes mellitus type ii".ti OR "dm type 2".ti OR "dm type ii".ti OR "T2D".ti OR (("type 2".ti OR "type2".ti OR "type two".ti OR "type ii".ti OR "typeii".ti) AND (diabete*.ti OR diabetic*.ti OR diabet*.ti))) AND ("low carbohydrate diet"/ OR "Carbohydrate-Restricted".mp OR "Carbohydrate Restricted".mp OR "Carbohydrates-Restricted".mp OR "Carbohydrates Restricted".mp OR Carbohydrate Restrict*.mp OR Carbohydrates Restrict*.mp OR "carbohydrate free".mp OR "carbohydrates free".mp OR carbohydrate free*.mp OR carbohydrates free*.mp OR "Low Carbohydrate".mp OR "Low Carbohydrates".mp OR Low Carbohydrat*.mp OR "South Beach Diet".mp OR "South Beach Diets".mp OR "Atkins Diet".mp OR Atkins Diet*.mp OR low carb*.mp OR "low fat diet"/ OR "low fat".mp OR low fat*.mp OR "Fat-Restricted".mp OR "Fat Restricted".mp OR "Fats-Restricted".mp OR "Fats Restricted".mp OR Fat-Restrict*.mp OR Fat Restrict*.mp OR "Low-Fat".mp OR "Low Fat".mp OR Low-Fat*.mp OR Low Fat*.mp OR "Fat-Free".mp OR "Fat Free".mp OR "Fats-Free".mp OR "Fats Free".mp OR Fat-Free*.mp OR Fat Free*.mp OR Fats-Free*.mp OR Fats Free*.mp) AND (exp "Randomized Controlled Trial"/ OR "RCT".mp OR random*.mp OR exp "Clinical Trial"/)) **OR** ((*"non insulin dependent diabetes mellitus"/ OR "type 2 diabetes".ti

OR "Ketosis-Resistant Diabetes".ti OR "Non-Insulin-Dependent Diabetes".ti OR "Stable Diabetes".ti OR "NIDDM".ti OR "Type 2 Diabetes".ti OR "Noninsulin-Dependent Diabetes".ti OR "Noninsulin Dependent Diabetes".ti OR "Type II Diabetes".ti OR "Type Two Diabetes".ti OR "Adult-Onset Diabetes".ti OR "Non-Insulin-Dependent Dm".ti OR "Stable Dm".ti OR "Type 2 Dm".ti OR "Noninsulin-Dependent Dm".ti OR "Noninsulin Dependent Dm".ti OR "Type II Dm".ti OR "Adult-Onset Dm".ti OR "Non-Insulin-Dependent Diabetic".ti OR "Type 2 Diabetic".ti OR "Noninsulin-Dependent Diabetic".ti OR "Noninsulin Dependent Diabetic".ti OR "Type II Diabetic".ti OR "Type Two Diabetic".ti OR "Adult-Onset Diabetic".ti OR "Type 2 Diabetics".ti OR "Noninsulin-Dependent Diabetics".ti OR "Noninsulin Dependent Diabetics".ti OR "Type II Diabetics".ti OR "Type Two Diabetics".ti OR "Adult-Onset Diabetics".ti OR "diabetes type 2".ti OR "diabetes type ii".ti OR "diabetes mellitus type 2".ti OR "diabetes mellitus type ii".ti OR "dm type 2".ti OR "dm type ii".ti OR "T2D".ti OR (("type 2".ti OR "type2".ti OR "type two".ti OR "type ii".ti OR "typeii".ti) AND (diabete*.ti OR diabetic*.ti OR diabet*.ti))) AND (exp "Carbohydrate Diet"/ OR "Carbohydrate Loading".mp OR "Carbohydrate-Rich".mp OR "Carbohydrate Rich".mp OR "Carbohydrates-Rich".mp OR "Carbohydrates Rich".mp OR rich carbohydrat*.mp OR "High Carbohydrate".mp OR "High Carbohydrates".mp OR High Carbohydrat*.mp OR high carb*.mp) AND (exp "Lipid Diet"/ OR "high fat".mp OR high fat*.mp OR "High-Fat".mp OR "High Fat".mp OR High-Fat*.mp OR High Fat*.mp) AND (exp "Randomized Controlled Trial"/ OR "RCT".mp OR random*.mp OR exp "Clinical Trial"/))) NOT conference review.pt
Search strategy for Academic Search Premier
fields searched: title, keyword, subject (("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))) AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*") AND ("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*"))
Search strategy for ScienceDirect
TITLE-ABSTR-KEY (("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant

Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D") AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*") AND ("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*") AND (trial* OR RCT* OR random* OR controlled))
Search strategy for LILACS
fields searched: title, abstract, subject ("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))) AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*") AND ("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*")
Search strategy for IBECS

fields searched: title, abstract, subject

("non insulin dependent diabetes mellitus" OR "type 2 diabetes" OR "Ketosis-Resistant Diabetes" OR "Non-Insulin-Dependent Diabetes" OR "Stable Diabetes" OR "NIDDM" OR "Type 2 Diabetes" OR "Noninsulin-Dependent Diabetes" OR "Noninsulin Dependent Diabetes" OR "Type II Diabetes" OR "Type Two Diabetes" OR "Adult-Onset Diabetes" OR "Non-Insulin-Dependent Dm" OR "Stable Dm" OR "Type 2 Dm" OR "Noninsulin-Dependent Dm" OR "Noninsulin Dependent Dm" OR "Type II Dm" OR "Adult-Onset Dm" OR "Non-Insulin-Dependent Diabetic" OR "Type 2 Diabetic" OR "Noninsulin-Dependent Diabetic" OR "Noninsulin Dependent Diabetic" OR "Type II Diabetic" OR "Type Two Diabetic" OR "Adult-Onset Diabetic" OR "Type 2 Diabetics" OR "Noninsulin-Dependent Diabetics" OR "Noninsulin Dependent Diabetics" OR "Type II Diabetics" OR "Type Two Diabetics" OR "Adult-Onset Diabetics" OR "diabetes type 2" OR "diabetes type ii" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "dm type 2" OR "dm type ii" OR "T2D" OR (("type 2" OR "type2" OR "type two" OR "type ii" OR "typeii") AND (diabete* OR diabetic* OR diabet*))) AND ("low carbohydrate diet" OR "Carbohydrate-Restricted" OR "Carbohydrate Restricted" OR "Carbohydrates-Restricted" OR "Carbohydrates Restricted" OR "Carbohydrate Restrict*" OR "Carbohydrates Restrict*" OR "carbohydrate free" OR "carbohydrates free" OR "carbohydrate free*" OR "carbohydrates free*" OR "Low Carbohydrate" OR "Low Carbohydrates" OR "Low Carbohydrat*" OR "South Beach Diet" OR "South Beach Diets" OR "Atkins Diet" OR "Atkins Diet*" OR "low carb*") AND ("low fat diet" OR "low fat" OR "low fat*" OR "Fat-Restricted" OR "Fat Restricted" OR "Fats-Restricted" OR "Fats Restricted" OR "Fat-Restrict*" OR "Fat Restrict*" OR "Low-Fat" OR "Low Fat" OR "Low-Fat*" OR "Low Fat*" OR "Fat-Free" OR "Fat Free" OR "Fats-Free" OR "Fats Free" OR "Fat-Free*" OR "Fat Free*" OR "Fats-Free*" OR "Fats Free*")

Supplemental Table 2 Ongoing studies (9)

Study name **ChiCTR-TRC-14004277**	A randomized controlled study to observe the effect of loosely low carbohydrate diet on metabolism with type 2 diabetes
Methods	Randomized controlled study Setting School of Nursing Soochow University, Jiansu, China Date of study January 2014 until July 2015. Study duration 3 months
Participants	N = 60 **Inclusion criteria of the trial** 1. Male or female patients aged 16 to 60 years old 2. Diagnosed as type 2 diabetes mellitus 3. HbA1c 7%~10% 4. SCr <123.2 μmol/L 5. No disorders of communication and understanding, willing and able to sign informed consent **Exclusion criteria of the trial** 1. Patients who were suffering from disorders of digestion, hepatic disease, severe complication, cancer, or malignant disease 2. History of instable cardiovascular disease or ketosis-prone diabetes
Interventions	**Intervention** Low carbohydrate for 3 months **Comparator** Routine diet for 3 months
Outcomes	Assessments: baseline and at 3 months **Primary outcome measures** 1. HbA1c 2. HDL-C 3. LDL-C **Secondary outcome measures** Nothing reported
Starting date	January 2014
Contact information	Xiaohua Wang, sxwang2001@163.com
Notes	Low carbohydrate diet: 39 en% carbohydrates, 19 en% protein, 42 en% fat Low-fat diet: 56 en% carbohydrates, 18 en% protein, 26 en% fat

Study name **ISRCTN05903336**	Pilot investigation into the effect of a low carbohydrate/high protein diet on cardiometabolic risk factors in obese patients with type 2 diabetes. An eight-week randomized controlled trial
Methods	Randomized controlled study Setting City Walls Medical Centre, Chester, UK Date of study February 2014 until October 2015. Study duration 8 weeks
Participants	N = 32 **Inclusion criteria of the trial** 1. Male or female, aged 18-75 2. BMI 28-40 kg/m² 3. HbA1c <86 mmol and a diagnosis of diabetes confirming to WHO guidelines 4. Stable medication at least three months prior to the study 5. Diabetes managed with Metformin or lifestyle only 6. English speaking with Internet access **Exclusion criteria of the trial** 1. History of eating disorder 2. Currently following a restrictive diet 3. Currently taking part in other research 4. Impaired kidney function 5. Impaired liver function 6. Patients taking medications to reduce blood clots 7. Pregnant women 8. Non-English speaking 9. No Internet access
Interventions	**Intervention** Low carbohydrate/high protein 'Dukan' diet for 8 weeks **Comparator** Low-fat 500-600 kcal energy-deficit diet for 8 weeks
Outcomes	Assessments (2): baseline and week 8 (secondary outcome measures also at week 4) **Primary outcome measures**

	1. Fasting plasma glucose/fasting plasma insulin 2. Glycosylated hemoglobin 3. Lipid profile (total serum cholesterol, HDL serum cholesterol, fasting serum triglycerides - from these LDL cholesterol and cholesterol/HDL ratio will also be calculated) 4. Kidney function (serum creatinine and urea, eGFR will then be calculated) 5. Liver function tests (gamma glutamyl transpeptidase, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, albumin, total protein, bilirubin) 6. Serum potassium, serum sodium, C-reactive protein 7. Serum ketones 8. Measures of oxidative stress (e-selectin, ICAM, vWF, MDA, 15-F2t isoprostane) **Secondary outcome measures** 1. Anthropometric measures of height, weight and waist circumference, measured using methods outlined in the Manual of Dietetic Practice 2. Blood pressure
Starting date	03-02-2014, completed 07-10-2015
Contact information	Dr Sohail Mushtaq Department of Clinical Sciences and Nutrition University of Chester Parkgate Road Chester CH1 4BJ United Kingdom
Notes	The trialists do not intend to publish this study as an article as they failed to recruit the required number of subjects to reach statistical significance. As a result the data generated (other than the results summaries) will not be made available

Study name **ISRCTN68494994**	Low carbohydrate nutrition in the treatment of type 2 diabetes: A randomized controlled trial on the glycemic effects of a low carbohydrate diet in comparison to a diet upon the recommendations of the clinical practice guideline (high-carb, low-fat)
Methods	Randomized controlled study Setting Rehab clinic in North Rhine-Westphalia, Germany Date of study

Online Supporting Material (OSM) – Supplemental Table 2

	March 2011 until June 2014. Study duration 24 weeks
Participants	N = 164 **Inclusion criteria of the trial** 1. Newly arrived inpatient of a selected rehab clinic (indications: cardiology, orthopedic) in North Rhine-Westphalia, Germany 2. Pre-diagnosed type 2 diabetes 3. Age of 18 years and above, either sex 4. Written consent **Exclusion criteria of the trial** 1. No type 2 diabetes 2. Renal insufficiency (creatinine of 2.5 mg/dl and above) 3. Pregnancy 4. Consuming disease 5. Rudimental / poor literacy (German)
Interventions	**Intervention** Low carbohydrate diet for 24 weeks **Comparator** Low-fat diet for 24 weeks During their rehabilitation, study participants experience theoretical lessons and a practical training in nutrition according to their diet-plan
Outcomes	Assessments (3): baseline, weeks 3 and 24 **Primary outcome measures** 1. HbA1c 2. Fasting blood glucose **Secondary outcome measures** Surrogate markers: 1. Insulin level 2. Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR) 3. Creatinine 4. Glomerular filtration rate 5. Body weight 6. Body-mass-index 7. Waist circumference 8. Serum lipid levels [total-, high density lipoprotein (HDL)-, low density lipoprotein (LDL)-cholesterol, triglyceride]

	Survey data: 1. Diabetes-medication (type and dose rate) 2. Diabetes treatment satisfaction (DTSQs/DTSQc) 3. Satisfaction with the diet (self constructed) 4. Quality of life (WHO-5) 5. Physical activity* (inpatient rehab data [t2], Freiburger Fragebogen zur körperlichen Aktivität [t3])
Starting date	March 2011 until October 2013, further follow-up until May 2014
Contact information	Jan Karoff, jkaroff@rehaforschung-koenigsfeld.de Universität Witten/Herdecke Office: Holthauser Talstraße 2 Ennepetal 58256 Germany +49 (0)2333 9888 484
Notes	Low carbohydrate diet: 25 en% carbohydrates, 30 en% protein, 45 en% fat Low-fat diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat

Study name **NCT00593424**	Effect of Changing the Diet to Low Fat/High Carbohydrate or High Monounsaturated Fat/Low Carbohydrate on Fasting and Post Fat Load Lipoproteins of Diabetics With Moderate Hypertriglyceridemia
Methods	Randomized, cross-over study, double-blind Setting VA Medical Center, Minneapolis, US Date of study August 2002 until November 2005. Study duration 6 weeks
Participants	N = 15 **Inclusion Criteria** 1. Male and female 2. 18 - 75 years of age 3. Type 2 diabetes 4. Fasting triglycerides 300 -800mg/dL

	Exclusion criteria None reported
Interventions	**Intervention** Low Fat/High Carbohydrate for 6 weeks **Comparator** High Monounsaturated Fat/Low Carbohydrate for 6 weeks
Outcomes	Assessments (2): baseline and 6 weeks **Primary Outcome Measures** 1. Paired t-test or Wilcoxon signed rank test will be used to evaluate the change in fasting triglycerides with the diets **Secondary Outcome Measures** 1. Post-prandial lipids will be evaluated by t-test or Wilcoxon signed rank test for AUC of triglyceride and remnant lipoprotein measured by immunoseparation
Starting date	August 2002
Contact information	Debra L Simmons, M.D., University of Arkansas, US. Currently working at Utah Hospital debra.simmons@hsc.utah.edu
Notes	No Study Results Posted

Study name **NCT00607867**	Metabolic Response to a LoBAG30 Diet in Diabetic Patients on Metformin
Methods	Randomized controlled study, open label Setting VA Medical Center, Minneapolis, US Date of study April 2008 until March 2011. Study duration 5 weeks
Participants	N = 20 **Inclusion criteria** 1. People with type 2 diabetes mellitus who currently are receiving the maximal dose of metformin monotherapy (2500 mg/day). 2. These subjects will have had a stable glycohemoglobin (tGHb) in an unacceptably high range (8-11%) for at least 4 months prior to beginning the study. 3. Subjects with tGHB > 11% (HbA1c > 10%) will not be recruited into the study.

	Exclusion criteria 1. Hematological abnormalities 2. Liver disease 3. Kidney disease 4. Macroalbuminuria (>300 mg albumin/24 hours) 5. Untreated thyroid disease 6. Congestive heart failure 7. Angina 8. Life-threatening malignancies 9. Proliferative retinopathy 10. Severe diabetic neuropathy 11. Peripheral vascular disease 12. Serious psychological disorders 13. A body mass index > 35 14. A fasting triglyceride of >400 mg/dl. 15. Subjects taking slow-release metformin will not be studied 16. Subjects taking medications other than metformin, known to affect fuel metabolism such as: insulin, the sulphonylureas, glucagon-like peptide 1 (GLP-1) analogs and metabolic inhibitors, pramlintide, prednisone and similar steroids, thyroid hormone, antipsychotic medications, thiazide diuretics, medroxyprogesterone, high dose aspirin, also will be excluded
Interventions	**Intervention** LoBAG30 for 5 weeks **Comparator** Control diet for 5 weeks
Outcomes	Assessments (2): baseline and week 5 **Primary Outcome Measures** 1. Change in % Hemoglobin A1c at 5 weeks from baseline 2. Change in total glucose area at 5 weeks from baseline 3. Change in body weight at 5 weeks from baseline 4.Change in overnight fasting glucose concentration at 5 weeks from baseline **Secondary Outcome Measures** 1. Microalbumin excretion 2. Change in fasting triglycerides at 5 weeks from baseline

Starting date	April 2008, study completing date March 2011
Contact information	Mary Gannon
Notes	LoBAG30 diet: 30 en% carbohydrates, 30 en% protein, 40 en% fat Control diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat The funding ended before the study was completed. "Funding ended with only 14 subjects studied. With a parallel arm design, we were not able to draw any conclusions from the study. Funds were unavailable for a more sophisticated statistical analysis"

Study name **NCT00931034**	The Effect of South Beach Diet™ Using South Beach Diet™ Products Compared to the American Diabetic Association Diabetes Meal Plan on Body Weight and Satiety in Overweight Diabetic Women
Methods	Randomized controlled study, open label Setting Multicenter US Date of study March 2007 until April 2008. Study duration 24 weeks
Participants	N = 120 **Inclusion criteria of the trial** 1. Female age 18 to 55 years 2. Females of childbearing potential must agree to use a medically approved method of birth control and have a negative urine pregnancy test result 3. Healthy as determined by laboratory results and medical history 4. Waist circumference > 87 cm 5. Stable weight defined as < 4.5 kg gained or lost in past year 6. Agreement to maintain current level of physical activity throughout the study 7. Diagnosed with Type II diabetes mellitus with fasting blood glucose 100 - 250 mg/dl (5.6 - 13.9 mmol/L) 8. Ability to comprehend and complete the questionnaires and forms 9. Agreement to comply with study procedures, test article consumption, and has access to a microwave oven 10. Voluntary, written, informed consent to participate in the study **Exclusion criteria of the trial** 1. Pregnant, breastfeeding, or planning to become pregnant during the course of the trial 2. Use of prescription or over the counter products known to effect weight including but not limited to the following: megestrol acetate;somatropin;sibutramine;orlistat;paroxetine;dextroamphetamine;methylphenidate;atomoxetine;quetiapine;olanzapine;risp

	eridone, within 4 weeks of randomization and during the trial 3. Unstable medication for diabetes mellitus (Dosage must be stable for 90 days prior to randomization), use of insulin is exclusionary 4. Alcohol use > 2 standard alcoholic drinks per day 5. Significant cardiac history defined as a history of: myocardial infarction (MI); coronary angioplasty or bypass graft(s); valvular disease or repair; unstable angina pectoris; transient Ischemic attack (TIA); cerebrovascular accidents (CVA); congestive heart failure; or coronary artery disease (CAD) 6. History of or current diagnosis of any cancer (except for successfully treated basal cell carcinoma) diagnosed less than 5 years prior to screening. Subjects with cancer in full remission for more than 5 years are acceptable. 7. Uncontrolled hypertension defined as untreated systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg 8. Unstable renal and/or liver disease 9. History of alcohol or drug abuse within the past year 10. Unstable psychiatric disorder requiring hospitalization within the past 6 months 11. Immunocompromised individuals such as subjects that have undergone organ transplantation or subjects diagnosed with human immunodeficiency virus (HIV) 12. History of hemoglobinopathies such as sickle cell anemia or thalassemia, sideroblastic anemia 13. Participation in another clinical research trial within 30 days prior to randomization and during the trial 14. Significant abnormal liver function as defined as AST and/or ALT > 2 x ULN, and/or bilirubin > 2 x ULN 15. Serum creatinine > 125 μmol/L 16. Anemia of any etiology defined as hemoglobin < 110 g/L 17. Uncontrolled and/or untreated thyroid disorder 18. Unstable medications (Dosage must be stable for 90 days prior to randomization) 19. History of food allergies or sensitivities, including lactose intolerance 20. Vegetarians 21. Cognitively impaired and/or unable to give informed consent 22. Any other condition which in the Investigator's opinion may adversely affect the subject's ability to complete the study or its measures or which may pose significant risk to the subject
Interventions	**Intervention** South Beach Diet with South Beach Diet Products for 24 weeks **Comparator** American Diabetes Association Diabetes Meal Plan for 24 weeks
Outcomes	Assessments (2): baseline and week 24

	Primary outcome measures 1. Change in body weight **Secondary outcome measures** 1. Assess the satiety response to the individual diets 2. Analyze circumference measurements & body composition; blood glucose, HbA1c, insulin, lipid profile, blood pressure & questionnaire responses on food cravings and quality of life
Starting date	March 2007, completed July 2008
Contact information	Study Director: David Crowley, KGK Synergize Inc
Notes	No data published, we have asked for data, but did not receive these (see contact with investigators). South Beach matches low carb, and ADA diet matches low fat diet

Study name **NCT02717078**	A Low Biologically Available Glucose and High Protein Diet for Treatment of Type 2 Diabetes Mellitus
Methods	Randomized controlled study, open label Setting University of Minnesota, United States Date of study Still recruiting. Study duration 12 weeks
Participants	N = 24 **Inclusion criteria** 1. 18 years of age or older 2. Diagnosis of type 2 diabetes mellitus 3. Hemoglobin A1c of 7.5-9.5% 4. Taking no medications for diabetes or taking metformin **Exclusion criteria** 1. Type 1 diabetes mellitus 2. Treatment with insulin 3. BMI <27 kg/m2 4. Change in weight of more than 5 pounds in the prior 3 months 5. Serum creatinine >1.5 mg/dL 6. Urine albumin >300 mg/g creatinine

	7. Pregnancy or immediate plans to become pregnant 8. Breast feeding 9. Dietary restriction(s) that would preclude consumption of the LoBAG diet 10. Inability or unwillingness to prepare meals 11. Presence of any disease which would make adherence to the study protocol difficult
Interventions	**Intervention** Low Biologically Available Glucose (LoBAG) Diet for 12 weeks **Comparator** Control diet (consistent with current Diabetes Association guidelines) for 12 weeks
Outcomes	Assessments (3): baseline, weeks 6 and 12 **Primary Outcome Measures** 1. Hemoglobin A1c **Secondary Outcome Measures** 1. Weight 2. Fasting plasma glucose 3. Fasting serum insulin 4. Plasma glucose and serum insulin before and after a meal 5. Fructosamine 6. Fasting serum lipids 7. Analysis of gut microbiome
Starting date	December 2016
Contact information	Anne Bantle, MD
Notes	LoBAG diet: 20 en% carbohydrates, 30 en% protein, 50 en% fat Control diet: 45-65 en% carbohydrates, 15-20 en% protein, 25-35 en% fat These percentages are estimates from previous publications, we are not sure what exact percentages will be used in the study as these are not reported

Study name **NCT02764021**	Cut Down on Carbohydrate Usage in the Diet of Type 2 Diabetes; Mechanisms of Effective Therapy of Diabetes by Selective Choice of Macronutrients. The Isoenergetic Study
Methods	Randomized controlled, cross-over study, open label Setting

	Bispebjerg Hospital, Copenhagen, Denmark Date of study Still recruiting. Study duration 42 weeks
Participants	N = 30 **Inclusion criteria** 1.Written informed consent signed before any study-specific procedure 2. Type 2 diabetes with glycated hemoglobin (HbA1c) between 48 mmol/mol and 97 mmol/mol with or without oral antidiabetic medicine 3. Age > 18 years, men and women 4. Hemoglobin > 7 mmol/L for men and > 6 mmol/L for women 5. Estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m2 **Exclusion criteria** 1. Critical illness 2. Systemic corticosteroid treatment e.g. prednisolone 3. Reported or journalized severe food allergy or intolerance 4. Reported or journalized severe gut disease e.g. Crohn's disease, Coeliac disease etc 5. Reported or journalized alcohol dependence syndrome 6. Injectable diabetes medication 7. Repeated fasting plasma glucose > 13.3 mmol/l 8. Urine albumin / creatinine ratio > 300 mg/g 9. Lactation, Pregnancy or planning of pregnancy during the study 10. Inability, physically or mentally, to comply with the procedures required by the study protocol, as evaluated by the principal investigator 11. Blood donation < 1 month prior to the study and during the study
Interventions	**Intervention** Carbohydrate-Restricted diet for 12 weeks **Comparator** Standard Antidiabetic diet for 12 weeks
Outcomes	Assessments (5): baseline, weeks 6, 12, 36 and 42 **Primary Outcome Measures**: 1. Changes in glycated hemoglobin (HbA1c) at the end of 6 weeks of isoenergetic low carbohydrate diet compared to 6 weeks of the recommended antidiabetic control diet

	Secondary Outcome Measures 2. Changes in heart rate variability (HRV) 3. Changes in diurnal blood pressure (DBP) 4. Changes in insulin sensitivity 5. Changes in beta-cell function 6. Changes in glucagon-like-petide-1 (GLP-1) 7. Changes in glucose-dependent insulinotropic polypeptide (GIP) 8. Changes in insulin-like growth factor-1 (IGF-1) 9. Changes in insulin-like growth factor-binding protein 1 (IGFBP-1) 10. Changes in growth hormone (GH) 11. Changes in cholecystokinin (CCK) 12. Changes in peptide YY (PYY) 13. Changes in ghrelin 14. Changes in liver, skeletal muscle and visceral fat composition 15. Changes in subjective satiety 16. Changes in anxiety and depression symptoms 17. Changes in insulin 18. Changes in C-peptide 19. Changes in non-esterified fatty acids (NEFA) 20. Changes in blood glucose 21. Changes in insulin-like growth factor-binding protein 3 (IGFBP-3)
Starting date	January 2018
Contact information	Mads GJ Skytte, MD, msky0019@regionh.dk Amirsalar Samkani, MD, asam0017@regionh.dk
Notes	Carbohydrate-Restricted diet: 30 en% carbohydrates, 30 en% protein, 40 en% fat Standard Antidiabetic diet: 50 en% carbohydrates, 13 en% protein, 17 en% fat

Study name **NCT03068078**	A Reduced-carbohydrate Diet High in Monounsaturated Fats in Type 2 Diabetes: a Six-month Study of Changes in Metabolism, Liver- and Cardiovascular Function (ReDuCtion)
Methods	Randomized controlled study, open label Setting

	Odense University Hospital, Odense, Denmark Date of study Still recruiting. Study duration 6 months
Participants	N = 135 **Inclusion criteria** 1. Duration of established T2D for more than six months and less than five years and HbA1c in compliance with T2D (above 48 mmol/mol), but without need for adjustment of antidiabetic treatment 2. Serum cholesterol below 4.5 mmol/l and LDL cholesterol below 2.5 mmol/l at inclusion 3. Age of 18 or above 4. Stable diabetic treatment three months prior to inclusion 5. Be able to read and understand Danish language 6. Signed written consent 7. Based on the assumption that metabolic and cardiovascular changes are less likely to be reversible in patients with longstanding T2D. HbA1c and need for adjustment and if the patient is eligible for inclusion will be evaluated individually based on the patients current treatment and current HbA1c by the project responsible. If the patient has duration of diabetes > 5 years but with current treatment ≤ 2 oral antidiabetic drugs and without insulin treatment, the patient will be accepted for enrolment. To avoid changes in lipid-lowering treatment during follow-up total cholesterol should be below 4.5 mmol/l and LDL cholesterol below 2.5 mmol/l at inclusion. Higher levels may be accepted if the patient cannot tolerate lipid-lowering treatment. Patients can be enrolled three months after medication change **Exclusion criteria** 1. Low carbohydrate diet prior to inclusion 2. Hypoglycemic unawareness 3. Excessive weight loss within the last three months, defined as more than 10 kilograms 4. Current treatment with glucocorticoids (systemic) 5. Continuous treatment with steatosis-inducing drugs (e.g. carbamazepine) 6. Treatment with antibiotics up to 2 months before inclusion* 7. Treatment with chemotherapy 8. Pregnancy or expected pregnancy within the next 6 months 9. Active alcohol overuse** 10. Active cancer 11. Significant co morbidity including liver disease 12. Poor compliance *Participants can be rescheduled to be included 2 months after use of antibiotics ** Prior alcohol overuse and eligibility will be evaluated individually

Online Supporting Material (OSM) – Supplemental Table 2

Interventions	**Intervention** Low carbohydrate diet, high in monounsaturated fats for 6 months **Comparator** Regular Diabetes diet for 6 months
Outcomes	Assessments (2): baseline and month 6 **Primary Outcome Measures** 1. Glycemic control measured by HbA1c 2. Dyslipidemia measured in plasma 3. Metabolic markers in type 2 diabetes mellitus **Secondary Outcome Measures:** 1. Endothelial function assessed by FMD in the brachial artery as well as microvascular damage assessed by retinal scan, urine albuminuria and minimal forearm vascular resistance (MFVR) 2. Non-Alcoholic Fatty Liver Disease (NAFLD) [assessed by a reduction in NAFLD Activity Score on liver biopsy and markers of inflammation and fibrogenesis. 3. Quality of life assessed by questionnaire 4. Gut dysbiosis assessed by fecal sample
Starting date	May 2016
Contact information	Eva Gram-Kampmann, MD, Eva.Gram-Kampmann@rsyd.dk
Notes	The regular diabetes diet is a low fat

Supplemental Table 3 Characteristics of excluded studies

Study	Reason for exclusion
Andersen 1987 (15)	Both diets appear to contain similar percentages of carbohydrates (45% and 48%) and fat (31% and 41%)
Aude 2004 (16)	There were only two patients with diabetes in one arm and zero in the other arm and only 3rd phase would meet the criteria and there was no wash-out time between phase 2 and 3
Brehm 2009 (17)	The high-carbohydrate diet matches our inclusion criteria for low fat diet, but the high-MUFA diet contains too much carbohydrate (45%)
Brunerova 2007 (18)	The conventional diet (low-fat) matches our inclusion criteria, but the high-monounsaturated-fat diet contains too much (45%) carbohydrate percentage (according to our inclusion criteria)
Chang 2016 (19)	Having diabetes was an exclusion criterion
Cullinen 2005 (20)	After reading full text not a study, but short review
Daly 2006 (21)	The low-carb diet matches our inclusion criteria, but the actual intake of fat percentage (32.9%) in the low fat diet is too high (according to our inclusion criteria)(post dietary assessment). The limits in energy percentages were not established beforehand!
Dansinger 2005 (22)	Overweight or obese patients were included "with known hypertension, dyslipidemia, or fasting hyperglycemia." and "current use of oral medication to treat hypertension, diabetes mellitus, or dyslipidemia". However, it is unclear whether people with diabetes were actually included, and if so how many in which groups
Delbridge 2009 (23)	Both diets appeared to be low fat diets
De Luis 2009 (24)	Study in overweight people but without diabetes
Due 2017 (25)	All three diets appeared to have > 40 en% of carbohydrates (actual dietary composition)
Dyson 2007 (26)	Both diets (low carbohydrate and healthy eating diet) are matching our inclusion criteria for low carbohydrate diets (17.3% vs 39.3%), and none of the two diets had a < 30 en% of fat
Esposito 2014 (27)	The low-fat diet matches our inclusion criteria, but the low carb diet contains too much (<50%) carbohydrate percentage (according to our inclusion criteria)
Fabricatore 2011 (28)	The low-fat diet matches our inclusion criteria, but the aim of the low GL diet was not < 40 en% of carbohydrates and the actual intake of carbohydrates in the low GL diet at 20 weeks appeared to be 46% which is too high (according to our inclusion criteria)(based of food records)
Foster 2010 (29)	After reading full text, it appeared that diabetes type 2 was an exclusion criterion
Gallagher 1987 (30)	Both diets appear to contain same percentage of carbohydrates (39%) and fat (41%)
Gannon 2003 (31)	Both diets appeared to be low fat diets

Gerhard 2004 (32)	The low-fat diet matches our inclusion criteria, but the low carb diet contains too much (45%) carbohydrate percentage (according to our inclusion criteria)
Goldstein 2011 (33)	The Atkins diet (low carbohydrate) matches our inclusion criteria, but the diet prescription specifies a low fat diet containing a minimum of 35% en% of fat which is too high (according to our inclusion criteria)
Haimoto 2014 (34)	Groups were not comparable at baseline (different HbA1c) and diets were according to HbA1c, two low carb diet groups but not a low fat diet group according to out inclusion criteria
Heilbronn 1999 (35)	The study compares three diets, a high carbohydrate diet and high-monounsaturated-fat (high MUFA) diet and a high saturated fat diet. The high-carbohydrate diet was enough low fat matching our inclusion criteria, but the carbohydrate percentage in high-monounsaturated-fat diet is too high (49.5%)as well as in the high saturated fat diet (52.2%) (according to our inclusion criteria)(based on food records)
Kimura 2018 (36)	Both diets appear to contain similar percentage of fat (30-35%) and (20-25%)
Kirk 2009 (37)	After reading full text, it appeared that diabetes type 2 was an exclusion criterion
Lee 2013 (38)	Conference abstract, not enough information on the diets
Ma 2008 (39)	Both diets appear to contain similar percentages of carbohydrates (around 38% at 12 months) and fat (42% and 43% at 12 months)
Maiorino 2016 (40)	The low-fat diet matches our inclusion criteria, but the low carb diet contains too much (<50%) carbohydrate percentage (according to our inclusion criteria)
McAuley 2006 (41)	Study in overweight people but without diabetes
McCargar 1998 (42)	The high monounsaturated fatty acid product (low carb) matches or inclusion criteria, but the high carbohydrate (low fat) product contained too (30.5%) fat percentage (according to our inclusion criteria)
McLaughlin 2007 (43)	The high carb (low-fat diet) matches our inclusion criteria, but the actual intake in the low carb diet contained too much (45%) carbohydrate percentage (according to our inclusion criteria)(based on food diary records from the entire study period)
Mesci 2010 (44)	Not enough info on percentages of carbohydrate, fat and protein content of both diets
Milne 1994 (45)	All diets do not match our inclusion criteria (too much carbohydrate and too much fat)
Nicholson 1999 (46)	Not a study comparing low carb versus low fat
O'Brien 1993 (47)	After reading full text, it appeared that both study periods of the cross-over study just lasted two weeks
Qi 2012 (48)	Study in overweight people but without diabetes
Radulian 2005 (49)	Abstract never published in full. Not clear what the cut-off values are for low carbohydrate diet and low fat diet
Rasmussen 1995 (50)	Intervention duration too short (3 weeks), cross-over study

Rock 2014 (51)	The low-fat diet matches our inclusion criteria, but the low carb diet contains too much (45%) carbohydrate percentage (according to our inclusion criteria)
Rodríguez-Villars 2000 (52)	The low-fat diet matches our inclusion criteria, but the high-fat, high–monounsaturated fatty acid diet (MONO diet), diet contains too much (45.3%) carbohydrate percentage (according to our inclusion criteria)
Saslow 2014 (53)	The very low-carb diet matches our inclusion criteria, intentions of the moderate carbohydrate diet also aimed for rather low carbohydrate en% (45-50% and to lower the fat consumption but no en% is specified. The actual intake of fat percentage (35.1%) in the medium-carb diet appeared to be too high (according to our inclusion criteria)(based on 24-hour food recall questionnaire) and the en% of carbohydrates appeared to be 40.7 almost matching our criterion for low carb, therefore we felt this was not a fair comparison of low carb versus low fat diet matching our criteria
Sato 2016 (54)	The routine diet matches our inclusion criteria (low-fat), and the intentions of the low carbohydrate diet (<130 g/day were good, but en% were not further specified and the actual intake in the low carb diet contained too much (46%) carbohydrate percentage (according to our inclusion criteria)(based on 3 day-food records)
Schwarz 2016 (55)	Not a study comparing diets
Shige 2000 (56)	The high-carbohydrate diet was enough low fat matching our inclusion criteria, but the high-monounsaturated-fat diet (MONO) contains too much (50%) carbohydrate percentage (according to our inclusion criteria)
Thomsen 1995 (57)	The low-fat diet matches our inclusion criteria, but the high-fat, high–monounsaturated fatty acid diet contains too much (45%) carbohydrate percentage (according to our inclusion criteria)
Vanninen 1994 (58)	Both diets did not match our inclusion criteria for low carbohydrate diet or low fat diet
Vlachos 2011 (59)	Abstract never published in full. Not clear what the cut-off values are for low-carbohydrate and protein sparing modified fast diets (PSMF) and low glycemic index diet
Walker 1999 (60)	The high-CHO (low fat) diet matches our inclusion criteria, but the actual intake of carbohydrates in the high-monounsaturated-fat diet (MONO) is too high (43.4%%)(according to our inclusion criteria)(based on three seven-day weighed food records)
Westman 2008 (61)	The very low-carb diet matches our inclusion criteria, but the control diet is not intended to reduce fat and the actual intake of the fat percentage (36%) in the low-glycemic index diet is too high (according to our inclusion criteria)(based on food records)

Supplemental Table 4 Included studies with no usable data

Study ID	Interventions & comparisons	N	Comments
Blades 1995 (62)	High-monounsaturated fat (low-carbohydrate) diet vs high-carbohydrate (low fat) diet	10	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Chen 1995 (64)	Low carbohydrate diet vs low fat diet	9	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Coulston 1989 (65)	Low carbohydrate diet vs low fat diet	8	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Garg 1988 (69)	High-monounsaturated fat (low carbohydrate) diet vs high-carbohydrate (low fat) diet	10	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Garg 1992 (70)	High-monounsaturated fat (low carbohydrate) liquid formula diet vs high-carbohydrate (low fat) liquid formula diet	10	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Garg 1994 (71)	High-monounsaturated fat (low carbohydrate) diet vs high-carbohydrate (low fat) diet	42	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Iqbal 2010 (76)	Low-carbohydrate diet vs low fat diet	144	Although the study intended in the Method section to meet our inclusion criteria for the diets, the actual intake of fat at 6 months in low fat diet group is 36.6 en% fat and at 12 months 36.4 en% fat and at 2 years 33.3 en% fat which exceeds at each time point the cut-off we set at 30% or lower
Jones 1986 (77)	Low-carbohydrate diet vs high-carbohydrate (low fat) diet	10	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Lopez-Espinoza 1984 (79)	Low carbohydrate diet vs modified fat (low fat) diet	59	None of our outcomes were assessed
Lousley 1983 (80)	Low carbohydrate diet vs high-carbohydrate-high fibre (low fat) diet	15	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks

Ney 1982 (82)	Control (low carbohydrate) diet vs high-carbohydrate (low fat) diet	20	Study includes both patients with type 1 and type 2 diabetes. No separate data
Rodríguez-Villar 2004 (85)	High-monounsaturated fat (low carbohydrate) diet vs high-carbohydrate (low fat) diet	26	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Samaha 2003 (86)	Low-carbohydrate diet vs low fat diet	132	At 6 months the actual intake of fat was 33% in the low fat diet group, which exceeded the 2 en% limit of excess we would accept (see Methods section). Furthermore, data are reported on some outcomes for diabetics (glucose, insulin and Hb1Ac), but it is unclear how many diabetic patients were left in each intervention group as we know there was a 40% drop out but no mentioning about how many diabetics dropped out in each intervention group, making it impossible for us to analyze the data
Saslow 2017 (87)	Very low carbohydrate diet vs control diet (low fat)	25	The actual intake of fat in the control plate at 16 and 32 weeks is 38.3 en% and 34.1 en% respectively, which exceeds the cut-off we set for the low fat diet
Shah 2005 (88)	High cis-monounsaturated fat (low carbohydrate) diet vs high-carbohydrate (low fat) diet	41	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Simpson 1979 (90)	Low-carbohydrate diet vs high-carbohydrate (low fat) diet	18	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Simpson 1981 (91)	Low-carbohydrate diet vs high-carbohydrate (low fat) high leguminous and cereal fibre diet	18	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Simpson 1982 (92)	Low-carbohydrate diet vs high-carbohydrate (low fat) diet	10	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks
Ward 1982 (95)	Low-carbohydrate diet vs high-carbohydrate (low fat) diet	7	Cross-over study and no separate data for the two separate study periods. No adequate wash-out period of at least 4 weeks

Supplemental Table 5 Duplicate studies of included and excluded studies

References to studies (studies that have been published more than once, or had evaluated other outcomes from the same study population)

Included studies	
Bozzetto 2012 (63)(2 additional refs)	1) Bozzetto L, Annuzzi G, Costabile G, Costagliola L, Giorgini M, Alderisio A, Strazzullo A, Patti L, Cipriano P, Magione A, et al. A CHO/fibre diet reduces and a MUFA diet increases postprandial lipaemia in type 2 diabetes: no supplementary effects of low-volume physical training. Acta Diabetol 2014;51:385-93. 2) Bozzetto L, Costabile G, Luongo D, Naviglio D, Cicala V, Piantadosi C, Patti L, Cipriano P, Annuzzi G, Rivellese AA. Reduction in liver fat by dietary MUFA in type 2 diabetes is helped by enhanced hepatic fat oxidation. Diabetologia 2016;59:2697-2701.
Davis 2009 (66) (4 additional refs)	3) 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. South Med J 2008;101(1):46-9. 4) Davis NJ, Crandall JP, Gajavelli S, Berman JW, Tomuta N, Wylie-Rosett J, Katz SD. Differential effects of low-carbohydrate and low-fat diets on inflammation and endothelial function in diabetes. J Diabetes Complications 2011;25:371-6. 5) Davis NJ, Tomuta N, Isasi C, Wylie-Rosett J. Effects of a low carbohydrate compared to a low fat diet on glycemic control in type 2 diabetes. J Gen Intern Med 2006;21(Suppl):46. 6) 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. Diabetes Educ 2012;38:250-5.
Elhayany 2010 (68) (2 additional refs)	7) 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;51:1616-22. 8) Shahar DR, Abel R, Elhayany A, Vardi H, Fraser D. Does dairy calcium intake enhance weight loss among overweight diabetic patients? Diabetes Care 2007;30:485-9.
Garg 1988 (69) (2 additional refs)	9) Garg A, Bonanome A, Grundy SM, Unger RH, Breslau NA, Pak CY. Effects of dietary carbohydrates on metabolism of calcium and other minerals in normal subjects and patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1990;70:1007-13.

	10) Shah M, Adams-Huet B, Grundy SM, Garg A. Effect of a high-carbohydrate vs a high-cis-monounsaturated fat diet on lipid and lipoproteins in individuals with and without type 2 diabetes. Nutrition Research 2004;24:969-79.
Guldbrand 2012 (73) (4 additional refs)	11) Guldbrand H, Lindström T, Dizdar B, Bunjaku B, Östgren CJ, Nystrom FH, Bachrach-Lindström M. 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 Res Clin Pract 2014;106:221-7. 12) Jonasson L, Guldbrand H, Lundberg AK, Nystrom FH. Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann Med 2014;46:182-7. 13) Lindström T, Bahrach-Lindström M, Guldbrand H, Dizdar B, Bunjaku B, Östgren , Nystrom FH. Randomisation to a low-carbohydrate diet improves health related quality of life compared with a low-fat diet at similar weight loss in type 2 diabetes. Diabetologia 2013;56(Suppl 1):S347. 14) Nystrom FH, Östgren CJ, Lindström T, Bahrach-Lindstrom M, Schöld A-K, Dizdar B, Frederikson M, Guldbrand H. A high fat diet improves glycaemic control compared with low fat diet: a24-month randomised prospective study of patients with type 2 diabetes in primary health care. Diabetologia 2011;54(Suppl 1):358.
Iqbal 2010 (76) (1 additional ref)	15) Vetter ML, Wade A, Womble LG, Dalton-Bakes C, Wadden TA, Iqbal N. Effect of a low-carbohydrate diet versus a low-fat, calorie-restricted diet on adipokine levels in obese, diabetic participants. Diabetes Metab Syndr Obes 2010;13:357-61.
Nielsen 2005 (83) (3 additional refs)	16) Nielsen JV, Jönsson E, Nilsson AK. Lasting improvement of hyperglycaemia and bodyweight: low-carbohydrate diet in type 2 diabetes--a brief report. Ups J Med Sci 2005;110:69-73. 17) Nielsen JV, Joensson E. Low-carbohydrate diet in type 2 diabetes. Stable improvement of bodyweight and glycemic control during 22 months follow-up. Nutr Metab (Lond) 2006;3:22. 18) Nielsen JV, Joensson EA. Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. Nutr Metab (Lond) 2008;5:14.
Nutall 2012 (84) (1 additional ref)	19) Gannon MC, Nuttall FQ. Effect of a high-protein diet on ghrelin, growth hormone, and insulin-like growth factor-I and binding proteins 1 and 3 in subjects with type 2 diabetes mellitus. Metabolism 2011;60:1300-11.

Samaha 2003 (86) (2 additional refs)	20) Seshadri P, Iqbal N, Stern L, Williams M, Chicano KL, Daily DA, McGrory J, Gracely EJ, Rader DJ, Samaha FF. A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. Am J Med 2004;117:398-405. 21) Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778-85.
Shai 2008 (89) (9 additional refs)	22) 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 Res Clin Pract 2009;86(Suppl 1):S41-8. 23) Canfi A, Gepner Y, Schwarzfuchs D, Golan R, Shahar DR, Fraser D, Witkow S, Greenberg I, Sarusi B, Vardi H, et al. Effect of changes in the intake of weight of specific food groups on successful body weight loss during a multi-dietary strategy intervention trial. J Am Coll Nutr 2011;30:491-501. 24) Gepner Y, Canfi A, Schwarzfuchs D, Golan R, Shahar D, Fraser D, Witkow S, Greenberg I, Vardi H, Sarusi B, et al. Effect of changes in the intake of specific food groups on weight loss; a two year dietary intervention trial. Diabetologia 2010;53(Suppl 1):S375. 25) Golan R, Tirosh A, Schwarzfuchs D, Harman-Boehm I, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Shai I of the DIRECT group. Dietary intervention induces flow of changes within biomarkers of lipids, inflammation, liver enzymes, and glycemic control. Nutrition 2012;28:131-7. 26) Paz-Tal O, Canfi A, Marko R, Katorza E, Karpas Z, Schwarzfuchs D, Shai I, Sheiner EK. Dynamics of magnesium, copper, selenium and zinc serum concentrations for 2-year dietary intervention. e-Spen J 2013;8:e100-7. 27) Paz-Tal O, Canfi A, Marko R, Katorza E, Karpas Z, Shai I, Sheiner EK. Effect of changes in food groups intake on magnesium, zinc, copper, and selenium serum levels during 2 years of dietary intervention. J Am Coll Nutr 2015;34:1-14. 28) Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. Obstet Gynecol Surv 2008;63:713-4. 29) Shai I. The effect of low-carb, Mediterranean and low-fat diets on renal function; a 2-year dietary intervention randomized controlled trial (DIRECT). Obes Facts 2012;5(Suppl 1):19.

	30) Tirosh A, Golan R, Harman-Boehm I, Henkin Y, Schwarzfuchs D, Rudich A, Kovasan J, Fiedler GM, Blüher M, Stumvoll M, et al. Renal function following three distinct weight loss dietary strategies during 2 years of a randomized controlled trial. Diabetes Care 2013;36:2225-32.
Tay 2014 (93) (7 additional refs)	31) Brinkworth GD, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert G, Wilson CJ. Long-term effects of very low-carbohydrate and high-carbohydrate weight-loss diets on psychological health in obese adults with type 2 diabetes: randomized controlled trial. J Intern Med 2016;280:388-97. 32) Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, Yancy WS, Brinkworth GD. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr 2015;102:780-90. 33) Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, Yancy W, Brinkworth GD. Long-term effects of a low carbohydrate, low saturated fat diet versus a conventional high carbohydrate, low fat diet in type 2 diabetes: a randomised trial. Diabetes Res Clin Pract 2014;106(Suppl 1):S34. 34) Tay J, Thompson CH, Luscombe-Marsh ND, Noakes M, Buckley JD, Wittert GA, Brinkworth GD. Long-term effects of a very low carbohydrate compared with a high carbohydrate diet on renal function in Individuals with type 2 diabetes: a randomized trial. Medicine (Baltimore) 2015;94:e2181. 35) Tay J, Zajac IT, Thompson CH, Luscombe-Marsh ND, Danthiir V, Noakes M, Buckley JD, Wittert GA, Brinkworth GD. A randomised-controlled trial of the effects of very low-carbohydrate and high-carbohydrate diets on cognitive performance in patients with type 2 diabetes. Br J Nutr 2016;116:1745-53. 36) Wycherley TP, Thompson CH, Buckley JD, Luscombe-Marsh ND, Noakes M, Wittert GA, Brinkworth GD. Long-term effects of weight loss with a very-low carbohydrate, low saturated fat diet on flow mediated dilatation in patients with type 2diabetes: A randomised controlled trial. Atherosclerosis 2016;252:28-31. 37) Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD, Wittert GA, Yancy WS Jr, Brinkworth GD. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial.Diabetes Obes Metab. 2018;20:858-871.

Walker 1995 (94) (1 additional ref)	38) Walker KZ, O'Dea K, Johnson L, Sinclair AJ, Piers LS, Nicholson GC, Muir JG. Body fat distribution and non-insulin-dependent diabetes: comparison of a fiber-rich, high-carbohydrate, low-fat (23%) diet and a 35% fat diet high in monounsaturated fat. Am J Clin Nutr 1996;63:254-60.
Wolever 2008 (96) (2 additional refs)	39) Wolever TM, Mehling C, Chiasson JL, Josse RG, Leiter LA, Maheux P, -Lhoret R, Rodger NW, Ryan EA. Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of carbohydrates in diabetes): a randomised controlled trial. Diabetologia 2008;51:1607-15. 40) Wolever TM, Chiasson JL, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. Effects of Changing the Amount and Source of Dietary Carbohydrates on Symptoms and Dietary Satisfaction Over a 1-Year Period in Subjects with Type 2 Diabetes: Canadian Trial of Carbohydrates in Diabetes (CCD). Can J Diabetes 2017;41:164-176.
Yamada 2014 (97) (1 additional ref)	41) Yamada S, Yamada Y, Irie J. A non-calorie-restricted non-ketogenic low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Diabetes 2013;Conference: 73rd Scientific Sessions of the American Diabetes Association. Chicago:July 2013:A192.
Excluded studies	
Dyson 2007 (27) (1 additional ref)	42) Dyson PA, Beatty S, Matthews DR. An assessment of low-carbohydrate or low-fat diets for weight loss at 2 year's follow-up. Diabet Med 2010;27:363-4.
Gannon 2003 (32) (3 additional refs)	43) Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. Diabetes 2004;53:2375-82. 44) Nuttall FQ, Gannon MC, Saeed A, Jordan K, Hoover H. The metabolic response of subjects with type 2 diabetes to a high-protein, weight-maintenance diet. J Clin Endocrinol Metab 2003;88:3577-83. 45) Nuttall FQ, Gannon MC. The metabolic response to a high-protein, low-carbohydrate diet in men with type 2 diabetes mellitus. Metabolism 2006;55(2):243-51.
Radulian 2005 (49) (1 additional ref)	46) 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.

Supplemental Table 6 Characteristics of included studies and risk of bias assessment, all details
Blades 1995 (62)

Methods	Randomized controlled, cross-over study Setting General Clinical Research Center of the University of Texas, Southwestern Medical Center, Dallas, US Date of study Unspecified. Study duration 6 weeks, 9 days washout and then cross-over for 6 weeks
Participants	N = 10 (all men) Mean age: 61.3 years (range 55-68 years) **Inclusion criteria of the trial** 1. Non-insulin-dependent diabetes mellitus 2. Fasting plasma glucose concentrations between 5.6 and 11.1 mmol/L 3. Fasting serum triacylglycerol concentrations < 5.64 mmol/L **Exclusion criteria of the trial** 1. Lipid lowering medications < 2 months prior to study entry Withdrawals/losses to follow-up None reported Baseline data (SD) BMI (kg/m²): 28.6 (2.7) Mean fasting plasma glucose (mmol/L): 8.8 (1.6) Mean fasting triacylglycerol concentrations (mmol/L): 2.07 (0.58) Mean fasting plasma cholesterol (mmol/L): 5.92 (0.84) Mean LDL cholesterol (mmol/L): 4.20 (0.91) Mean HDL cholesterol (mmol/L): 0.85 (0.84) Mean HbA1c (%): 9.2 (2.0)
Interventions	**Intervention** • High-monounsaturated-fat (low carbohydrate) diet for 6 weeks, 9 days washout and then cross-over for 6 weeks **Comparator** • High-carbohydrate diet (low fat) for 6 weeks, 9 days washout and then cross-over for 6 weeks All patients ate at least one meal, i.e. breakfast, lunch, or dinner, at the metabolic unit on weekdays. The food for the rest of the day was supplied in packages to be consumed at home. The individual food items were weighed daily during meal preparation and all meals were prepared in metabolic kitchen. Olive oil was used as the main source of fat in the high-monounsaturated-fat diet. The energy intake of each patient was adjusted if needed to maintain constant body weight during the study. Both study diets consisted of natural foods. Energy intake was constant during the two study diets (10.0± 0.8 and 10.0 ± 0.8 MJ with the high-monounsaturated-fat diets and high-carbohydrate respectively; 10 MJ = 2388 kcal). The patients were instructed not to consume alcohol and not to change their usual physical activity during the study.
Outcomes	Assessments (3): baseline, last 3d of each dietary period of 6 weeks **Primary outcome measures** 1. Oral-fat tolerance test 2. Triacylglycerol and retinyl palmitate concentrations ✱ 3. Postheparin lipase test **Secondary outcome measures** 1.Fasting plasma total cholesterol, VLDL, HDL and LDL ✱

	✱ Denotes outcomes prespecified for this review
Funding source	Quote page 996: "Supported in part by grants M0l-RR00633 and HL-29252 from the National Institutes of Health, Bethesda, MD, and Pfizer Pharmaceuticals, New York."
Declaration of interest	None declared
Notes	Medication: all patients were taking 17.8 ± 13 mg glipizide/d (Glucotrob; Pfizer Inc. NY); this dosage was kept constant throughout the study except when a patient reported symptomatic hypoglycemia, at which time the dosage was reduced by 2.5 mg/d High-monounsaturated-fat (low carbohydrate) diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat High-carbohydrate (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Data from both study periods are pooled and no separate data per study period are available. Wash-out period is 9 days, which is considered too short. Study is more than 20 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table Blades 1995 (62)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 996 and 997): "randomized" and "The study was a randomized, crossover design". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians and all food during the study period was provided by the metabolic kitchen, and they were instructed not to consume alcohol and not to change physical activity during the study. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was a too short wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the

		nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Bozzetto 2012 (63)

Methods	Randomized controlled study Setting Department of Internal Medicine of the University Medical School Hospital, Federico II University, Naples, Italy Date of study September 2009 until September 2011. Study duration 8 weeks
Participants	N = 45 (37 men, 8 women) Mean age (SD): MUFA group 57 (8) years, CHO/fiber group 58 (5) years, MUFA+Ex group 59 (9) years, CHO/fiber+Ex group 63 (5) years **Inclusion criteria of the trial** 1. Men and postmenopausal women with type 2 diabetes 2. Age 35-65 years 3. BMI 27- 34 kg/m2 without body weight changes over the previous 6 months 4. HbA1c <8% 5. Fasting plasma cholesterol <200 mg/dl 6. Fasting plasma triglycerides <150 mg/dl **Exclusion criteria of the trial** 1. Hypolipidemic drugs 2. Plasma creatinine >1.7 mg/dl transaminases > 2 normal values 3. Ischemic heart disease or positive treadmill stress test 4. High intensity regular physical activity 5. Any disease or chronic or/and acute condition contraindicating physical activity (anemia, and infectious, neoplastic, neurological and osteoarticular diseases) Withdrawals/losses to follow-up 9/45 (20%); • 4: one in each group due family reasons or could no longer accomplish their work commitments • 5: refused proton nuclear magnetic resonance (^{1}H NMR) spectroscopy examination because of claustrophobia Baseline data (SD) BMI (kg/m^2): MUFA group 28 (3), CHO/fire group 30 (2), MUFA+Ex group 29 (2), CHO/fiber+Ex group 31 (3) Body weight (kg): MUFA group 79 (13), CHO/fiber group 85 (13), MUFA+Ex group 87 (13), CHO/fiber+Ex group 83 (13) Waist circumference (cm): MUFA group 100 (8), CHO/fiber group 103 (6), MUFA+Ex group 104 (11), CHO/fiber+Ex group 101 (8), HbA1c (%): MUFA group 6.6 (0.8), CHO/fiber group 6.3 (0.3), MUFA+Ex group 6.9 (0.6), CHO/fiber+Ex group 6.7 (0.9) Fasting plasma cholesterol (mg/dl): MUFA group 171 (25), CHO/fiber group 155 (39), MUFA+Ex group 165 (33), CHO/fiber+Ex group 172 (38) Fasting plasma triglyceride (mg/dl): MUFA group 122 (38), CHO/fiber group 114 (71), MUFA+Ex group 92 (29), CHO/fiber+Ex group 97 (30) Fasting plasma glucose (mg/dl): MUFA group 145 (37), CHO/fire group 137 (15), MUFA+Ex group 136 (15), CHO/fiber+Ex group 133 (27)

	Fasting plasma LDL cholesterol (mg/dl): MUFA group 110 (20), CHO/fiber group 98 (29), MUFA+Ex group 110 (29), CHO/fiber+Ex group 116 (36) Fasting plasma HDL cholesterol (mg/dl): MUFA group 35 (6), CHO/fiber group 37 (8), MUFA+Ex group 40 (7), CHO/fiber+Ex group 44 (11)
Interventions	The intervention was preceded by a run in period of 3 weeks during which participants were stabilized on a diet with a composition similar to the one usually followed, only providing that saturated fatty acids were at least 13% (carbohydrate 48%, total fat 33%, saturated fat 13%, and protein 18% of total energy intake) **Intervention** • High-MUFA (low carbohydrate) diet (MUFA group) for 8 weeks (n = 8) **Comparator 1** • High-carbohydrate, high-fiber, low-glycemic index (low fat) diet (CHO/fiber group) for 8 weeks (n = 9) **Comparator 2** • High-MUFA (low carbohydrate) diet plus physical training (MUFA+Ex group) for 8 weeks (n = 9) **Comparator 3** • High-carbohydrate, high-fiber, low-glycemic index (low fat) diet plus physical training (CHO/fiber+Ex group) for 8 weeks (n = 10) The dietary macronutrient composition was drawn by the tables of food composition from the Italian National Research Institute for Food and Nutrition. For improvement of dietary compliance, patients were seen weekly by an experienced dietitian, who made telephone calls every 2–3 days to ensure that they followed the assigned diet. The experimental diets were isoenergetic in order to keep body weight constant and differed in macronutrient composition Total energy intake (kcal/day): MUFA group 2039 (431), CHO/fiber group 1873 (407), MUFA+Ex group 2480 (362), CHO/fiber+Ex group 2037 (456) The structured supervised exercise program was performed at the Cardiac Rehabilitation Centre of the Department of Translational Medical Sciences. Participants exercised on treadmill or cycle ergometer two times per week for 45 min at an intensity corresponding to 70% of their baseline peak VO2
Outcomes	Assessments (2): baseline and week 8 **Primary outcome measures** 1. Liver fat content (^{1}H NMR) spectroscopy examination) 2. HbA1c ✱ 3. Fasting plasma glucose ✱ 4. Fasting plasma triglyceride ✱ 5. Fasting plasma cholesterol 6. Fasting lipoprotein fractions ✱ 7. Anthropometrics (body weight, height, and waist circumference) ✱ 8. Cardiorespiratory fitness **Secondary outcome measures** 1. Adherence to the dietary treatments was evaluated by a 4-day food record (two weekend and two working days) completed by the participants every second week ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 1434: "The work presented here was supported by ETHERPATHS project (European Community contract no. FP7-KBBE-222639). L.B. received a research grant from the Italian Diabetes Society: "Borsa di studio annuale SID-AMD Pasquale Di Coste."

Declaration of interest	Quote page 1434: "No potential conflicts of interest relevant to this article were reported"
Notes	Medication: 26/45 used metformin in addition to diet High-MUFA (low carbohydrate) diet: 40 en% carbohydrates, 18 en% protein, 42 en% fat (fiber 10 g/1000 kcal), actual intake 40 en% carbohydrates, 18 en% protein, 42 en% fat High-carbohydrate (low fat) diet: 52 en% carbohydrates, 18 en% protein, 30 en% fat (fiber 28 g/1000 kcal), actual intake 53 en% carbohydrates, 19 en% protein, 28 en% fat. We only included the first two treatment arms, without the supervised exercise training as our objective is comparing diets

Risk of bias table of Bozzetto 2012 (63)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1430): "The allocation to the intervention, stratified for BMI, age, sex, and diabetes therapy (only diet or metformin),was randomly performed by a minimization method using MINIM software". Comment: Probably done.
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: There was insufficient information to permit a clear judgement. After email communication: "The assignment to the treatment was performed using the MINIM software by a person not directly involved in the study execution. This software assigned by chance each subject to the treatment group according to stratification variables (BMI, age, sex, and diabetes therapy). This was done at each enrolment and, therefore, there was no list of allocation, which the investigators could use to predict the following group assignments.*"* Comment: Form of central allocation.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1430): "All evaluations were performed before and after the 8-week intervention periods by personnel blinded to the assignment". Comment: The report did not provide sufficient detail about the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement and participants were not blinded. After e-mail communication: "Images and blood samples were labelled with an alpha-numeric code indicating the sequence of enrolment of the participants, which was independent of the treatment assignment, and with a letter indicating if it was the first or second access (i.e. before or after intervention). Therefore, the personnel who made all evaluations at the end of the trial was blinded to the

		assignment." For improvement of dietary compliance, patients of all groups were seen weekly by an experienced dietitian, who made telephone calls every 2–3 days to ensure that they followed the assigned diet. Comment: Although outcome assessors were blinded, physicians and patients were not, and we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 1430): "All evaluations were performed before and after the 8-week intervention periods by personnel blinded to the assignment". Outcomes were investigator-assessed. Comment: The report provided sufficient detail about the measures used to blind personnel from knowledge of which intervention a participant received, to permit a clear judgement. Outcome measurements were objective and unlikely to be influenced.
Incomplete outcome data (attrition bias)	High risk	9/45 (20%), reasons provided. One from each group due family reasons or could no longer accomplish their work commitments. The other five unclear from which group. Per-protocol analysis. Comment: High number of drop-outs at follow-up combined with the per-protocol analysis poses a high risk of bias for this domain.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinical trials.gov (NCT01025856), and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Chen 1995 (64)

Methods	Randomized controlled, cross-over study, open-label Setting Stanford General Clinical Research Center, Palo Alto, California, US Date of study Unspecified. Study duration 6 weeks, followed by cross-over to other diet for 6 weeks. No mentioning of wash-out period between the 2 diets
Participants	N = 9 (6 men, 3 women) Mean age (SD): 49 (16) years **Inclusion criteria of the trial** 1. Participants with non-insulin dependent diabetes mellitus in otherwise good general health **Exclusion criteria of the trial** 1. Medication other than a sulphonylurea compound Withdrawals/losses to follow-up None reported Baseline data (SD)

	BMI (kg/m²): 27.5 (2.9) Fasting plasma glucose (mmol/L): 8.8 (1.5) Fasting plasma triglycerides (mmol/L): 5.6 (1.2)
Interventions	Before starting the test diet, all patients were instructed to follow a control diet, containing (as percentage of total calories) 15% protein, 40% fat, and 45% CHO for 14 days **Intervention** • Low carbohydrate diet for 6 weeks and then cross-over for 6 weeks **Comparator** • Low fat diet for 6 weeks and then cross-over for 6 weeks All food consumed during the study period was provided by the General Clinical Research Center kitchen. Patients came to the kitchen every evening for dinner and at that time were given the pre-packaged meals for breakfast and lunch the following day. Total daily caloric intake was calculated for each subject to achieve weight maintenance during the 6-week dietary periods. Diets were isocaloric
Outcomes	Assessments (3): baseline, weeks 6 and 12 **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Fasting plasma triglycerides ✱ 3. Retinyl ester concentrations 4. Very-low-density lipoprotein-TG turnover 5. Lipoprotein lipase measurement **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 15: "This study was supported by National Institutes of Health Grants HL-08506 and RR-00070"
Declaration of interest	None declared
Notes	No medication (other than a sulphonylurea compound) Low carbohydrate diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat Low fat diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Data from both study periods are pooled and no separate data per study period are available. No washout period. Study is more than 20 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Chen 1995 (64)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 10): "Patients with NIDDM were placed randomly on diets..". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.

Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians and all food during the study period was provided by the General Clinical Research Center kitchen. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at a high risk of bias.

Coulston 1989 (65)

Methods	Randomized controlled, cross-over study, open-label Setting Stanford General Clinical Research Center, Palo Alto, California, US Date of study Unspecified. Study duration 6 weeks, followed by cross-over to other diet for 6 weeks. No mentioning of wash-out period between the 2 diets
Participants	N = 8 (5 men, 3 women) Mean age (SE): 66 (3) years **Inclusion criteria of the trial** 1. Participants with non-insulin dependent diabetes mellitus in otherwise good general health **Exclusion criteria of the trial** 1. Medication other than a sulphonylurea compound Withdrawals/losses to follow-up None reported Baseline data (SE) BMI (kg/m²): 25.5 (0.8) Fasting plasma glucose (mmol/L): 10.5 (1) Fasting plasma triglycerides (mmol/L): 2.18 (0.27) Fasting plasma cholesterol (mmol/L): 5.88 (0.50)
Interventions	**Intervention** • Low carbohydrate diet for 6 weeks and then cross-over for 6 weeks **Comparator**

	• Low fat diet for 6 weeks and then cross-over for 6 weeks All food consumed during the study period was provided by the General Clinical Research Center kitchen. Total daily calorie intake was calculated for each subject to achieve weight maintenance.
Outcomes	Assessments (12): baseline and then weekly (not for all analyses) **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Fasting plasma triglycerides ✱ 3. Fasting cholesterol 4. Fasting and postprandial plasma samples on days 41 and 42 of each diet period at hourly intervals for determining glucose and insulin concentrations 5. Fasting VLDL, LDL, HDL at day 41 and 42 of each diet 6. 24 h urine collection on day 41 for glucose excretion **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 100: "This study was supported by NIH Research Grants RR-7022 and HL-08506 and the Nora Eccles Treadwell Foundation."
Declaration of interest	None declared
Notes	No medication, other than sulphonylureas Low carbohydrate diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat Low fat diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat Data from both study periods are pooled and no separate data per study period are available. No washout period. Study is more than 20 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Coulston 1989 (65)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 95): "...with two 6-wk dietary periods randomly assigned". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians and all food consumed by the subjects of during the 84- day period was provided by the General Clinical Research Center kitchen. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.

Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at a high risk of bias.

Davis 2009 (66)

Methods	Randomized controlled study, open label Setting Clinical Research Center of Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, US Date of study August 2004 until November 2006. Study duration 1 year
Participants	N = 105 (23 men, 82 women) Mean age: 55 years **Inclusion criteria of the trial** 1. > 18 years with a diagnosis of diabetes for at least 6 months 2. BMI ≧ 25 kg/m² 3. HbA1c between 6-11% **Exclusion criteria of the trial** 1. Weight change of 10 pounds within 3 months of screening 2. Kidney disease (defined as creatinine 1.3 mg/dl) 3. Active liver or gallbladder disease 4. Significant heart disease 5. A history of severe (requiring hospitalization) hypoglycemia 6. Or use of weight loss medications Withdrawals/losses to follow-up 14/105 (13.3%); 8/55 in the low carbohydrate diet group, 6/50 in the low fat diet group • Schedule conflicts: 3 in low carbohydrate diet group, 2 in the low fat diet group • Other illness: 1 in low carbohydrate diet group, 0 in the low fat diet group • Personal reasons: 1 in low carbohydrate diet group, 1 in the low fat diet group • Moved: 1 in low carbohydrate diet group, 1 in the low fat diet group • Unknown: 1 in low carbohydrate diet group, 1 in the low fat diet group Baseline data (SD) Weight (kg): low carbohydrate diet group 93.6 (18), low fat diet group 101 (19) BMI (kg/m²): low carbohydrate diet group 35 (6), low fat diet group 37 (6) Systolic blood pressure (mmHg): low carbohydrate diet group 125 (18), low fat diet group 130 (17)

	Diastolic blood pressure (mmHg): low carbohydrate diet group 73 (9), low fat diet group 77 (10) HbA1c (%): low carbohydrate diet group 7.5 (1.5), low fat diet group 7.4 (1.4) Total cholesterol (mmol/L): low carbohydrate diet group 4.4 (0.83), low fat diet group 4.3 (0.86) LDL (mmol/L): low carbohydrate diet group 2.5 (0.69), low fat diet group 2.4 (0.74) HDL (mmol/L): low carbohydrate diet group 1.3 (0.24), low fat diet group 1.2 (0.29) Triglycerides (mmol/L): low carbohydrate diet group 34 (62), low fat diet group 28 (56)
Interventions	**Intervention** • Low carbohydrate diet for 1 year (n = 55) **Comparator** • Low fat diet for 1 year (n = 50) The low-carbohydrate diet was modelled after the Atkins diet and the low-fat diet was modelled after that in the Diabetes Prevention Program. Participants were provided with general recommendations to achieve 150 min of physical activity each week. All participants received 45 min of individual dietary instruction by a registered dietitian and were given a specific gram allowance of carbohydrates or fat to achieve a 1-pound weight loss each week. Structured menus that provided meal choices and recipes were used for the first 2 weeks. After the first 2 weeks, participants were instructed on selecting foods that met their dietary goals without using the menus. During the 12-month study, participants had a total of six scheduled, 30-min visits with the dietitian for additional dietary counselling. Total energy intake at 6 months (kcal/day): low carbohydrate diet group 1652 (650), low fat diet group 1653 (471) Total energy intake at 12 months (kcal/day): low carbohydrate diet group 1642 (600), low fat diet group 1810 (590)
Outcomes	Assessments (4): baseline, months 3, 6 and 12 **Primary outcome measures** 1. Weight ✱ 2. Glycemic control (HbA1c) ✱ **Secondary outcome measures** 1. Blood pressure ✱ 2. Fasting serum lipids (total cholesterol, HDL, LDL, triglycerides) ✱ ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 1151-2: "This work was supported by research grants through the Robert C. Atkins Foundation and the Diabetes Research and Training Center (P60 DK020541) and by Clinical and Translational Science Award UL1 RR025750. We thank Bayer Pharmaceuticals and Sanofi Aventis for their donations. We thank Joy Pape for her advice and assistance."
Declaration of interest	Quote page 1152: "No other potential conflicts of interest relevant to this article were reported"
Notes	Medication: at randomization, the algorithm included reducing insulin dosages by 50% and discontinuing sulphonylurea in the low-carbohydrate arm and reducing insulin by 25% and decreasing the sulphonylurea dose by 50% in the low-fat arm. Subsequently, the algorithm for medication adjustment was the same in both groups. Adjustments of insulin and sulphonylurea were made based on results of self-monitored capillary blood glucose. Metformin was not adjusted during the study Low carbohydrate diet: 24 en% carbohydrates, 27 en% protein, 49 en% fat at 3 months, 33.5 en% carbohydrates, 22.5 en% protein, 43.0 en% fat (total adds up to 99%) at 6 months, 33.4 en% carbohydrates, 22.7 en% protein, 43.9 en% fat at 12 months

	Low fat diet: 53 en% carbohydrates, 22 en% protein, 25 en% fat at 3 months, 48.1 en% carbohydrates, 20.5 en% protein, 30.8 en% fat (total adds up to 99.4%) at 6 months, 50.1 en% carbohydrates, 18.9 en% protein, 30.8 en% fat (total adds up to 99.8%) at 12 months

Risk of bias table of Davis 2009 (66)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 1148): "By using a computer-generated 1:1 randomization, participants were assigned to either a low-carbohydrate or a low-fat diet." Comment: Probably done.
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: There was insufficient information to permit a clear judgement. After e-mail communication: "The allocation sequence was done by the statistician and the assignments were kept in numbered, opaque sealed envelopes by the statistician. The investigators did not know what the next randomization assignment would be. When participants came for their randomization visit, the sequentially numbered envelope was given to the research assistant. The research assistant learned of the assignment at the same time as the participant and the protocol was followed based on the assignment." Comment: Allocation appears to have been adequately concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Participants in each arm received a booklet with the carbohydrate or fat content of common foods and instructions for self-monitoring. Both groups received same recommendations to exercise. All participants received 45 min of individual dietary instruction by a registered dietitian and all participants had a total of six scheduled, 30-min visits during the 12 month period with the dietitian for additional dietary counselling. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Open label. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	14/105 (13.3%); 8/55 in low carbohydrate diet group, 6/50 in the low fat diet group. Reasons reported. Intention-to-treat analysis.

		Comment: Moderate number (balanced) of losses to follow-up combined with an intention-to-treat analysis judged as low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol of the study was available at clinical trial.gov (NCT00795691) and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

De Bont 1981 (67)

Methods	Randomized controlled study Setting Departments of Dietetics and Medicine, University Hospital of Wales, Cardiff, and Department of Dietetics, Royal Gwent Hospital, Newport, Wales, UK Date of study Unspecified. Study duration 6 months
Participants	N = 148 (all women) Mean age: 55 years **Inclusion criteria of the trial** 1. Age 35-64 years 2. Insulin independent diabetes type 2 3. Free of other diseases **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up 12/148 (8.1%) unclear from which group • Withdrawn by physician (6) • Withdrawn themselves (4) • One patient died • Total cholesterol at entry of the study was close to the upper limit of laboratory measurement and which at the end of the study exceeded that limit (1) Baseline data (SD) Weight (kg): low carb diet group 73 (16), low fat diet group 72 (15) Fasting plasma glucose (mmol/L): low carb diet group 9.7 (3.4), low fat diet group 9.1 (3.0) Fasting plasma HbA1c (%): low carb diet group 10.1 (2.4), low fat diet group 10.0 (2.4) Fasting triglycerides (mmol/L): low carb diet group 1.75, low fat diet group 1.87 Fasting HDL (mmol/L) low carb diet group 1.99, low fat diet group 1.96
Interventions	**Intervention** • Low carbohydrate diet for 6 months (n = 65) **Comparator** • Low fat diet for 6 months (n = 71) It is unclear how many in each group were of the 12 that were excluded from the analysis. No specific dietary regimes were used. Instead the dietitians reviewed the current diets of the patients. During the period of study all patients received three home visits from a single nutritionist who encouraged continued adaptation of diets towards the low fat or the low carbohydrate dietary targets. Dietary response was measured by one-day food intakes before dietary advice was given and again at the end of the study, using the 'weighed inventory method'. Weighing scales (Salter No. 50T) were supplied

	to each patient who was asked to weigh and record every food item to the nearest % oz (3.54 g). Dietary records were checked for completeness with the patient by the nutritionist. These visits were arranged for the same day of the week as the weighed record on entry. Visits were unannounced in order to improve the validity of the records
Outcomes	Assessments (2): baseline and at 6 months **Primary outcome measures** 1. Weight and height ✱ 2. Blood pressure every month ✱ 3. Fasting blood glucose and HbA1c ✱ 4. Fasting cholesterol, HDL-cholesterol, and triglycerides ✱ **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 533: "The late Mr. A. de Bont was supported by a Royal Society fellowship as part of the European Science Exchange Programme of the Royal Society London and the 'Netherlands Organization for the Advancement of Pure Research' (Z. W. O.)"
Declaration of interest	None declared
Notes	Diet only: low carb diet group 34%, low fat diet group 37%; diet plus oral hypoglycemic drugs: low carb diet group 65%, low fat diet group 62%; diet plus insulin: low carb diet group 2%, low fat diet group 1% Low carbohydrate diet: carbohydrates < 40 en%, actual intake at 6 months 38 en% carbohydrates, 19.9 en% protein, 41.8 en% fat (total add up to 99.7%) Low fat diet: fat < 30 en%, actual intake at 6 months 45.7 en% carbohydrates, 22.7 en% protein, 31.1 en% fat (total add up to 99.5%)

Risk of bias table of de Bont 1981 (67)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 529): "They were randomly allocated to receive advice for low fat or low carbohydrate diets from experienced hospital dietitians". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Both groups received counselling regarding their diets of dietitians. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.

Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	12/148 (8.1%) unclear from which group. Low number of drop-outs. Per-protocol analysis. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters. Comment: We judged this as at a low risk of bias.

Elhayany 2010 (68)

Methods	Randomized controlled study, open label Setting Urban primary care clinics (10) in Israel's central region, Israel Date of study March 2003 until April 2004. Study duration 1 year
Participants	N = 259 (93 men, 86 women, 80 gender unknown) Mean age: 55 years **Inclusion criteria of the trial** 1. Age 30-65 years 2. Diabetes type 2 diagnosed within 1-10 years 3. Body Mass Index (BMI) 27-34 kg/m² 4. Last HbA1c measurement 7-10% 5. Last plasma triglyceride level 1.8-4.5 mmol/L • 6. Last serum creatinine < 123.2 µmol/ 7. No change in diabetes medication for at least 3 months **Exclusion criteria of the trial** 1. Proliferative diabetic retinopathy 2. Current insulin treatment 3. Active oncologic or psychiatric disease 4. Uncontrolled hypothyroidism or hyperthyroidism Withdrawals/losses to follow-up 80/259 (30.9%); 24/85 in the low carb Mediterranean diet group, 30/85 in the low fat diet group, 26/89 in the traditional Mediterranean diet group • Non-compliance: 13 in the low carb Mediterranean diet group, 10 in the low fat diet group, 11 in the traditional Mediterranean diet group • Changed residence: 3 in the low carb Mediterranean diet group, 2 in the low fat diet group, 0 in the traditional Mediterranean diet group • Domestic problems: 4 in the low carb Mediterranean diet group, 3 in the low fat diet group, 0 in the traditional Mediterranean diet group • Unrelated health problems: 2 in the low carb Mediterranean diet group, 7 in the low fat diet group, 5 in the traditional Mediterranean diet group • Other: 2 in the low carb Mediterranean diet group, 2 in the low fat diet group, 1 in the traditional Mediterranean diet group • Incomplete 12- month follow-up data: 0 in the low carb Mediterranean diet group, 6 in the low fat diet group, 9 in the traditional Mediterranean diet group

Online Supporting Material (OSM) – Supplemental Table 6

	Baseline data (SD) Weight (kg): low carb Mediterranean diet group 86.7 (14.3), low fat diet group 87.9 (13.7), traditional Mediterranean diet group 85.5 (10.6) BMI (kg/m²): low carb Mediterranean diet group 31.4 (2.8), low fat diet group 31.8 (3.3), traditional Mediterranean diet group 31.1 (2.8) Waist circumference (cm): low carb Mediterranean diet group 112.7 (9.6), low fat diet group 113.4 (10.0), traditional Mediterranean diet group 11.1 (9.1) HbA1c (%): low carb Mediterranean diet group 8.3 (1.0), low fat diet group 8.3 (0.8), traditional Mediterranean diet group 8.3 (1.0) Fasting plasma glucose (mmol/L): low carb Mediterranean diet group 10.5 (2.0), low fat diet group 10.3 (1.7), traditional Mediterranean diet group 10.1 (1.8) Fasting plasma insulin (µU/ml): low carb Mediterranean diet group 13.5 (5.7), low fat diet group 12.7 (6.2), traditional Mediterranean diet group 12.1 (6.5) HOMA: low carb Mediterranean diet group 5.9 (4.0), low fat diet group 5.8 (3.3), traditional Mediterranean diet group 5.0 (2.9) Total cholesterol (mmol/L): low carb Mediterranean diet group 5.4 (0.9), low fat diet group 5.4 (0.9), traditional Mediterranean diet group 5.5 (0.8) HDL- cholesterol (mmol/L): low carb Mediterranean diet group 1.1 (0.2), low fat diet group 1.1 (0.2), traditional Mediterranean diet group 1.1 (0.2) LDL-cholesterol (mmol/L): low carb Mediterranean diet group 3.1 (0.8), low fat diet group 3.0 (0.8), traditional Mediterranean diet group 3.0 (0.7) Triglycerides (mmol/L): low carb Mediterranean diet group 3.2 (0.8), low fat diet group 3.1 (0.8), traditional Mediterranean diet group 3.0 (0.7)
Interventions	Prior to randomization, patients entered a 2-week maintenance period. During this time, the patients were asked to continue their usual diet and keep a food intake diary Completed 12 month follow-up: **Intervention** • Low carbohydrate Mediterranean diet for 1 year (n = 61) **Comparator 1** • Low fat diet for 1 year (n = 55) **Comparator 2** • Traditional Mediterranean diet for 1 year (n = 63) Patients were followed up by the same dietitian every 2 weeks for 1 year. All dieticians followed a structured protocol for the 24 scheduled meetings and treated patients from each of the three diet groups. All patients were advised to engage in 30–45 min of aerobic activity at least 3 days a week All 3 diets were isocaloric and kept at 20 calories per kg bodyweight
Outcomes	Assessments (26): baseline and every 2 weeks up to 1 year **Primary outcome measures** 1. Weight, height, waist and hip circumferences ✱ 2. Blood pressure every month ✱ 3. Fasting blood glucose, plasma insulin levels, HbA1c at baseline and every 3 months ✱ 4. Total cholesterol, HDL-C, triglycerides at baseline and every 3 months ✱ 5. Liver enzymes, serum creatinine and urea at baseline and every 3 months **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	None declared, but in the earlier published studies of 2007 and 2008 in the study populations mentioned "This study was supported by a grant from Tnuva Research Institute, Rehovot, Israel"

Declaration of interest	None declared
Notes	Medication: no details of medication during the study but no insulin Low carbohydrate Mediterranean diet: 35 en% carbohydrates, 20 en% protein, 45 en% fat, at 6 months the carbohydrate en% increased to 41.9% Low fat diet (ADA): 50 en% carbohydrates, 20 en% protein, 30 en% fat, at 6 months the carbohydrate en% was reduced to 45.4% Traditional Mediterranean diet: 50 en% carbohydrates, 20 en% protein, 30 en% fat, at 6 months the carbohydrate en% was reduced to 45.2% The food recall questionnaire at 6 months indicate that the carbohydrate energy percentage between low carbohydrate Mediterranean diet and the low fat (ADA) diet only differ for 3.5%, and we have no idea where these percentages end at 1 year Before the study, the dietitians participated in a training workshop to ensure standardization in questionnaire administration. 24-h food recall questionnaire, a validated food frequency questionnaire (FFQ) at baseline, month 3 and 6. Physical activity questionnaire, including quality of life measures at baseline, month 3 and 6

Risk of bias table of Elhayany 2010 (68)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote (page 205): "Of the 259 patients enrolled in the study, 85 were randomly assigned to the ADA diet, 89 to TM, and 85 to the LCM diet." In the study of Fraser 2008 which included the same population (see reference as copublication of same study with other outcome data under reference of Elhayany 2010) it states "using a systematic sequence" and "allocation by alternation". Comment: Quasi-randomized poses a high risk of bias.
Allocation concealment (selection bias)	Low risk	Quote (page 1617 of Fraser 2008): "allocation was performed centrally and both the potential participant and recruiter were blinded to the allocation procedure and its outcome." Comment: Central allocation. Allocation appears to have been adequately concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Patients were followed up by the same dietitian every 2 weeks for 1 year. All dieticians followed a structured protocol for the 24 scheduled meetings and treated patients from each of the three diet groups. All patients were advised to engage in 30–45 min of aerobic activity at least 3 days a week. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Unclear risk	Nothing reported regarding blinding. However, majority of outcome measurements were objective and unlikely to be influenced, but the questionnaires were subjective and therefore likely to be influenced

		Comment: We consider the risk of bias for this outcome to be unclear.
Incomplete outcome data (attrition bias)	High risk	80/259 (30.9%), balanced amongst groups. Comment: The high total number of dropouts although balanced between the groups, which, combined with a per-protocol analysis represents a high risk of bias.
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available at clinical trials.gov (NCT00520182).The prespecified outcomes and those mentioned in the methods section appeared to have been reported except for liver enzymes, serum creatinine and urea. Only baseline and 1 year values were reported. Comment: We judged this as at an unclear risk of bias.
Other bias	Unclear risk	There was no baseline imbalance between groups for any of the parameters. The 80 individuals who did not complete the 12-month follow-up had, at baseline, statistically significant higher fasting plasma glucose, total cholesterol and LDL-C levels than patients who completed the study. Comment: We judged this as an unclear risk of bias.

Garg 1988 (69)

Methods	Randomized controlled, cross-over study Setting General Clinical Research Center of the Parkland Memorial Hospital in Dallas, US Date of study Unspecified. Study duration 4 weeks and then an interval of 6 to 22 days between the 2 diets (diet of the American Diabetes Foundation) and then cross-over for 4 weeks
Participants	N = 10 (all men) Mean age (SE): 56 (2) years **Inclusion criteria of the trial** 1. Insidious onset of diabetes with minimal symptoms **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SE) Weight (kg): 88 kg BMI (kg/m²): 29 (3) Fasting plasma cholesterol (mmol/L): > 5.2 Fasting plasma triglycerides (mmol/L): > 2.3
Interventions	First week and during interval between two diets patients received the recommended American Diabetes Association diet (50 en% carbohydrates, 20 en% protein, 30 en% fat) **Intervention** • High-monounsaturated-fat (low carbohydrate) diet for 4 weeks, then a 1-3 week washout followed by cross-over for 4 weeks **Comparator** • High-carbohydrate (low fat) diet for 4 weeks, then a 1-3 week washout followed by cross-over for 4 weeks Interval of 6 to 22 days between the 2 diets. Patients were hospitalized. The meals were cooked in the metabolic kitchen of the General Clinical Research Center. The patients were instructed to maintain a constant level of physical activity (restricted to level walking) throughout the study.

	Energy intake (SE) (MJ): high-monounsaturated-fat (low carbohydrate) diet 10.12 (0.3), high-carbohydrate (low fat) diet 10.07 (0.3)
Outcomes	Assessments (14): baseline, day 21, daily on days 24-28 and then cross-over **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. HbA1c ✱ 3. Total cholesterol, triglycerides, VLDL, HDL, LDL ✱ 4. Free insulin 5. 24h urine **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 829: "Supported in art by grants (HL-29252, M01-RR00633, 5R01AM02700-28) from the National Institutes of Health, the Veterans Administration (549-8000, 549-8676), the Southwestern Medical Foundation, the European Economic Community, and the Moss Heart Foundation in Dallas"
Declaration of interest	None declared
Notes	Medication: throughout the study, all patients received a combination of neutral protamine Hagedorn (NPH) and regular human insulin subcutaneously before breakfast and supper High-monounsaturated fat (low carbohydrate) diet: 35 en% carbohydrates, 15 en% protein, 50 en% fat High-carbohydrate (low fat) diet: 60 en% carbohydrates, 15 en% protein, 25 en% fat Data from both study periods are pooled and no separate data per study period are available. Wash-out period is 6-22 days, which is considered too short. Study is almost 30 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table Garg 1988 (69)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 830): "A randomized crossover study was designed". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Patients were hospitalized. The meals were cooked in the metabolic kitchen of the General Clinical Research Center. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.

Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was a too short wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Garg 1992 (70)

Methods	Controlled, cross-over study Setting General Clinical Research Center of the Parkland Memorial Hospital in Dallas, US Date of study Unspecified. Study duration 4 weeks and then cross-over for 4 weeks
Participants	N = 10 (all men) Mean age (SE): 61.5 (1.3) years **Inclusion criteria of the trial** 1.Insidious onset of diabetes mellitus with minimal symptoms **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up One patient could not complete the study (urine tract infection) but was not excluded from the analysis Baseline data (SE) Weight (kg): 86.7 (4.4) BMI (kg/m²): 27.7 (1.2)
Interventions	Oral hypoglycemic drugs, if any, were discontinued at least 3 months before study, and the patients were in stable metabolic condition, as evidenced by body weights and glycemic control. During a baseline period of 2 -5 days, all patients received isocaloric mixed natural diet recommended by the American Diabetes Association diet (50 en% carbohydrates, 20 en% protein, 30 en% fat) **Intervention** • High-monounsaturated-fat diet (low carbohydrate) as a liquid formula for 4 weeks, and then cross-over for 4 weeks **Comparator** • High-carbohydrate diet (low fat) as a liquid formula for 4 weeks, and then cross-over for 4 weeks Patients were hospitalized. Energy intake was adjusted to maintain a constant body weight during the study. Patients were instructed to maintain a constant level of

	physical activity restricted to level walking and were advised not to engage in any form of strenuous physical activity throughout the study.
Outcomes	Assessments (8): baseline and days 14, 21 and 28 and then cross-over **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Fasting glucagon, and C-peptide 3. Fasting cholesterol, triglycerides, VLDL, HDL, LDL ✱ 4. GHb concentration 5. 24-h urine for glucose determination **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 1597: "This study was supported in part by National Institutes of Health Grants HL-29252, 5R01AM02700-28, DK-02700-29, and M01-RR00633, Veterans Administration Grants 549-8000 and 549-8676, the Southwestern Medical Foundation, Mead Johnson & Co., California Fats & Oils, Inc., and Procter & Gamble, Inc"
Declaration of interest	None declared
Notes	Medication: oral hypoglycemic drugs, if any, were discontinued at least 3 months before study High-monounsaturated fat (low carbohydrate) diet as a liquid formula: 38 en% carbohydrates, 17 en% protein, 45 en% fat High-carbohydrate (low fat) diet as a liquid formula: 65 en% carbohydrates, 15 en% protein, 20 en% fat Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is 25 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias of Garg 1992 (70)

Study ID	Bias due to confounding	Bias in selection of the participants in the study	Bias in measurement of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall bias
Garg 1992	Serious risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias

Garg 1994 (71)

Methods	Randomized controlled, cross-over study Setting Metabolic units of Stanford University School of Medicine, the university of Texas Southwestern Medical Center, Dallas, university of Minnesota, Minneapolis, and the Veterans Affairs Medical Center, San Diego, US Date of study Unspecified. Study duration 6 weeks and then an Interval of 7 days between the 2 diets and then cross-over for 6 weeks
Participants	N = 42 (33 men, 9 women) Mean age (SD): 58 (10) years **Inclusion criteria of the trial**

	1. Non-Insulin-Dependent Diabetes Mellitus **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported, however data of two persons were not included in the analyses (urine tract infection and missing blood sample) Baseline data (SD) BMI (kg/m²): 28.1 (2.9) Fasting plasma glucose (mmol/L): 5.6-11.1 Fasting triglyceride (mmol/L): 0.61-4.97
Interventions	**Intervention** • High-monounsaturated-fat diet (low carbohydrate) for 6 weeks, one week washout and then cross-over for 6 weeks **Comparator** • High-carbohydrate diet (low fat) for 6 weeks, one week washout and then cross-over for 6 weeks Standard diet menus for each study diet were prepared for an 8.4-MJ (2000-kcal) diet using foods available at all centers. For a different energy level, all food items were proportionately reduced or increased from the standard menu. Recipes and menus of various food items were standardized. A 4-day rotational menu was used. There was a median interval of 7 days between the two diet periods when the patients consumed their usual diets. To assess the longer-term effects of the diets, all patients were invited to consume the second diet for 8 additional weeks (phase 2 extension) without interruption. The patients were instructed not to change their usual physical activity during the study.
Outcomes	Assessments (4): baseline, weeks 6 and 13 and after the extension period **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Fasting cholesterol, triglycerides, VLDL, HDL, LDL ✱ 3. HbA1c ✱ **Secondary outcome measures** 1.Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote (Page 1427): "This study was supported in part by a grant from Pfizer Inc, New York, NY, the National Institutes of Health grants (M01-RR00633, M01-RR-00400, M01-RR-00827, M01-RR00070, HL-29252, HL-08506, and DK 38949), and the Medical Research Service of the San Diego (Calif) Veterans Affairs Medical Center."
Declaration of interest	None declared
Notes	Medication: all the patients were receiving glipizide therapy, and the dose of glipizide averaged 17 mg per day High-monounsaturated fat (low carbohydrate) diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat High-carbohydrate (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Data from both study periods are pooled and no separate data per study period are available. Wash-out period 7 days, which is too short. Study is 23 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Garg 1994 (71)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1422): "An independent randomization scheme was prepared for each center to decide the order of the study diets. Patients were randomized in blocks of 10 with equal numbers (five and five) assigned to the two diet orders". Comment: Probably done.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians and all food during the study period was provided by the metabolic kitchen. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Moderate number (balanced) of losses to follow-up combined with per-protocol analysis Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was a too short wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at a high risk of bias.

Goday 2016 (72)

Methods	Randomized controlled study, open label Setting Multicenter (6) Endocrinology departments of participating Centers across Spain Date of study Unspecified. Study duration 4 months
Participants	N = 89 (31 men, 58 women) Mean age (SD): 54.53 (8.37) years **Inclusion criteria of the trial**

	1. Age between 30-65 years 2. Previous diagnosis of type 2 diabetes 3. BMI between 30-35 kg/m² **Exclusion criteria of the trial** 1. Type 2 Diabetes > 10 years 2. Insulin therapy 3. HbA1c ≥ 9% and fasting C-peptide < 1 ng/ml 4. Impaired renal function (< 60 ml/min per 1.73 m²) 5. Impaired liver function (liver enzymes ≥ twofold upper normal limit) 6. Alcohol intake ≥ 40 g/day for men, and ≥24 g/day for women 7. Pregnancy 8. Severe eating or psychiatric disorder Withdrawals/losses to follow-up 13/89 (14.6%); 5/45 in very low-calorie-ketogenic diet group, 8/44 in low calorie (low fat) diet group Reasons not provided Baseline data (SD) Weight (kg): very low-calorie-ketogenic diet group 91.47 (11.43), low calorie (low fat) diet group 89.54 (11.37) BMI (kg/m²): very low-calorie-ketogenic diet group 33.25 (1.52), low calorie (low fat) diet group 32.88 (1.60) Waist circumference (cm): very low-calorie-ketogenic diet group 108.13 (8.55), low calorie (low fat) diet group 105.94 (8.49) HbA1c (%): very low-calorie-ketogenic diet group 6.89 (1.11), low calorie (low fat) diet group 6.88 (1.03) Cholesterol (mg/dl): very low-calorie-ketogenic diet group 200.1 (36.0), low calorie (low fat) diet group 199.4 (51.0) Triglycerides (mg/dl) very low-calorie-ketogenic diet group 150.5 (54.4), low calorie (low fat) diet group 176.1 (92.0) LDL cholesterol (mg/dl): very low-calorie-ketogenic diet group 112.7 (33.6), low calorie (low fat) diet group 109.8 (45.5) HDL cholesterol (mg/dl): very low-calorie-ketogenic diet group 55.9 (11.1), low calorie (low fat) diet group 55.1 (11.7)
Interventions	**Intervention** • Very low-calorie-ketogenic diet for 4 months (n = 45) **Comparator** • Low calorie (low fat) diet for 4 months (n = 44) The program included nine individual sessions and a telephone contact every 15 days in both study arms. Energy intake (kcal/day): very low-calorie-ketogenic diet 600–800 kcal per day, low calorie (low fat) diet 500–1000 kcal per day. The 4-month dietary intervention in subjects randomly assigned to the interventional weight loss following a VLCK diet (VLCK diet group) as part of a commercial weight-loss program (DiaproKal Method) based on a high biological-value protein preparations diet and natural foods. This method has three stages: active, metabolic stabilization and maintenance. This active stage is maintained until the patient loses most of weight loss target, ideally 90% (between 30 and 45 days). In the metabolic stabilization stage, the patients underwent a progressive incorporation of different food groups and participated in a program of alimentary re-education to guarantee the long-term maintenance of the weight lost. The maintenance stage consisted of an eating plan balanced in

	carbohydrates, protein and fat. The target was to maintain the lost weight and promote healthy life styles. The intervention for both groups included an evaluation by the specialist physician conducting the study, an assessment by an expert dietician, group meetings and exercise recommendations. Individual counselling to support lifestyle and behavioral modification throughout the study was performed according to a structured support program by an endocrinologist and a registered dietitian at each participating center in the low calorie diet group.
Outcomes	Assessments (4): baseline, week 2, months 2 and 4 **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. HbA1c, HOMA-IR ✱ 3. Fasting plasma triglycerides, total cholesterol, LDL cholesterol ✱ 4. Renal function, liver function, plasma uric acid, sodium and potassium 5. Body weight, BMI, waist circumference ✱ **Secondary outcome measures** 1. Dietary adherence and patient satisfaction (Eating Self-Efficacy Scale and Likert Scale (1 = very unsatisfied, 2 = unsatisfied, 3 = indifferent, 4 = satisfied, 5 = very satisfied)) ✱ Denotes outcomes prespecified for this review
Funding source	Quote (page 6): Editorial assistance was provided by Montse Vidal, Punta Alta Communication and funded by PronoKal Group. The founding for the study as well as the DiaproKal method products were provided by Pronokal Group., (Barcelona, Spain) free of charge to the patients. The funding source had no involvement in the study design, recruitment of patients, study interventions, the data collection or interpretation of the results. The investigators and representatives from Pronokal Group were responsible for the study design, protocol, statistical analysis plans, analysis and reporting of the results. Final responsibility for the decision to submit the manuscript for publication was made jointly by all author"
Declaration of interest	Quote page 6: "AG, DB, BM, ABC and FFC received advisory board fees and or research grants from Pronokal Protein Supplies Spain"
Notes	Medication: oral antidiabetic medication was taken as before and diminished or stopped during the study period Very low carbohydrate diet: < 50 g carbohydrates per day, no exact specification as energy percentages Low calorie (low fat) diet: 45-60 en% carbohydrates, 10-20 en% protein, < 30 en% fat (based on diet American Diabetes Association (ADA)). The low calorie diet was aimed at a daily energy restriction of 500–1000 kcal according to each individual's basal metabolic rate

Risk of bias of Goday 2016 (72)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 2): "Randomization to one of the two study groups was stratified by participating Center" and "The 4-month dietary intervention in subjects randomly assigned to the interventional weight loss". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. The intervention for both groups included an evaluation by the specialist physician conducting the study, an assessment by an expert dietician, group meetings and exercise recommendations. Individual counselling to support lifestyle and behavioral modification throughout the study was performed according to a structured support program by an endocrinologist and a registered dietitian at each participating center. The program included nine individual sessions and a telephone contact every 15 days in both study arms. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	13/89 (14.6%). Analysis of the safety and tolerability (safety population) variables was performed with an intention-to-treat analysis with baseline or last observation carried forward when the complete set of data for an individual was not available. Changes in body weight, BMI and waist circumference between groups were compared in the 'efficacy population', composed by those with at least one efficacy measurement available after randomization. Comment: Moderate number (balanced) of losses to follow-up judged as at an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters. Comment: We judged this as at a low risk of bias.

Guldbrand 2012 (73)

Methods	Randomized controlled study Setting Two primary health care centers in Motala and Borensberg, Sweden Date of study March 2009 until December 2011. Study duration 2 years
Participants	N = 61 (27 men, 34 women)

	Mean age (SD): 61.2 (9.5) years in the low card diet group, 62.7 (11) years in the low fat diet group **Inclusion criteria of the trial** 1. Type 2 diabetes treated with diet with or without additional oral glucose-lowering medication, incretin-based therapy or insulin **Exclusion criteria of the trial** 1. Difficulties understanding the Swedish language 2. Suffering from severe mental disease or malignant disease 3. Abusing drugs Withdrawals/losses to follow-up None reported Baseline data (SD) Weight (kg): low carb diet group 91.4 (19), low fat diet group 98.8 (21) BMI (kg/m²): low carb diet group 31.6 (5.0), low fat diet group 33.8 (5.7) Waist circumference (cm): low carb diet group 106 (15), low fat diet group 110 (13) HbA1c (%): low carb diet group 7.5 (3.1), low fat diet group 7.2 (2.9) Systolic blood pressure (mmHg): low carb diet group 135 (15), low fat diet group 136 (13) Diastolic blood pressure (mmHg): low carb diet group 76 (11), low fat diet group 77 (9) Total cholesterol (mmol/L): low carb diet group 4.5 (1.0), low fat diet group 4.3 (1.0) LDL-cholesterol (mmol/L): low carb diet group 2.7 (0.9), low fat diet group 2.4 (0.7) HDL-cholesterol (mmol/L): low carb diet group 1.13 (0.33), low fat diet group 1.09 (0.29) Triacylglycerols (mmol/L): low carb diet group 1.7 (1.4), low fat diet group 1.8 (0.8)
Interventions	**Intervention** • Low carb diet for two years (n = 30) **Comparator** • Low fat diet for 2 years (n = 31) Group information was used to inform the randomized patients about which food items to choose from, and this was given at baseline, and 2, 6 and 12 months by two different physicians. One dedicated dietitian provided the participants from both groups with suitable recipes at each group meeting, and was also available consecutively during the trial for questions from the participants Energy content for both diets: 1600 kcal/day for women, and 1800 kcal/day for men
Outcomes	Assessments (4): baseline, months 6, 12 and 24 **Primary outcome measures** 1. Anthropometrics (weight, BMI, waist circumference, sagittal abdominal diameters) ✱ 2. Laboratory tests (HbA1c, total cholesterol, LDL, HDL, triglycerides) ✱ 3. Blood pressure ✱ **Secondary outcome measures** 1. Questionnaires of quality of life (SF-36) ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 2126: "The study was supported by University Hospital of Linköping Research Funds, Linköping University, the County Council of Östergötland, and the Diabetes Research Centre of Linköping University."
Declaration of interest	Quote page 2126: "The authors declare that there is no duality of interest associated with this manuscript".
Notes	Medication: the physician responsible for each patient at the primary healthcare center was thus allowed to adjust hypolipidemic and antihypertensive medications consecutively in the trial

	Low carbohydrate diet: 20 en% carbohydrates, 30 en% protein, 50 en% fat, at 3-6 months 25 en% carbohydrates, 24 en% protein, 49 en% fat (total adds up to 98%), at 12 months 27 en% carbohydrates, 23 en% protein, 47 en% fat (total adds up to 97%), at 24 months 31 en% carbohydrates, 24 en% protein, 44 en% fat (total adds up to 99%) Low fat diet: 55-60 en% carbohydrates, 10-15 en% protein, 30 en% fat, at 3-6 months 49 en% carbohydrates, 21 en% protein, 29 en% fat (total adds up to 99%), at 12 months 47 en% carbohydrates, 20 en% protein, 31 en% fat (total adds up to 98%), at 24 months 47 en% carbohydrates, 20 en% protein, 31 en% fat (total adds up to 98%)

Risk of bias table of Guldbrand 2012 (73)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2119): "Randomisation was not stratified and was based on drawing blinded ballots". Comment: Probably done.
Allocation concealment (selection bias)	Low risk	Participants were randomized by drawing ballots as soon as they had accepted to participate after inclusion and exclusion criteria were checked. Comment: It was not possible to foresee allocation before enrolment.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. The interventions were based on four group meetings with a duration of 60 min each for the first year; no further group meetings during the remaining 12 months were held. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Unclear risk	Nothing reported regarding blinding. However, majority of outcome measurements were objective and unlikely to be influenced, but the questionnaires were subjective and therefore likely to be influenced. Comment: We consider the risk of bias for this outcome to be unclear.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol of the study was available at clinicaltrials.gov (NCT01005498) but outcomes were not prespecified, but those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Gumbiner 1998 (74)

Methods	Controlled study Setting Clinical Research Center (CRC) of the University of Rochester, New York, US Date of study

	Unspecified. Study duration 6 weeks. The study was divided into three phases: pre-diet, diet, and refeeding. We include data from the 2nd phase
Participants	N = 17 (8 men, 9 women) Mean age (SD): 53 (4) years **Inclusion criteria of the trial** 1. Obese volunteers with Non-Insulin-Dependent Diabetes Mellitus **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SE) Weight (kg): MUFA diet group 101.8 (5.4), high carbohydrate diet group 110.4 (8.6) BMI (kg/m²): MUFA diet group 36.3 (2.0), high carbohydrate diet group 37.2 (2.1) Fasting glucose (mmol/L): MUFA diet group 12.6 (1.1), high carbohydrate diet group 11.2 (0.7) Fasting insulin (pmol/L): MUFA diet group 114 (17), high carbohydrate diet group 130 (30) Total cholesterol (mmol/L)(95% CI): MUFA diet group 5.3 (0.4), high carbohydrate diet group 4.5 (0.4) LDL-cholesterol (mmol/L): MUFA diet group 3.1 (0.4), high carbohydrate diet group 2.5 (0.4) HDL-cholesterol (mmol/L): MUFA diet group 1.0 (0.1), high carbohydrate diet group 1 (0.1) Triglyceride (mmol/L): MUFA diet group 2.8 (0.4), high carbohydrate diet group 2.2 (0.2)
Interventions	The study was divided into three phases: pre-diet, diet, and refeeding. Upon completing the pre-diet phase, patients were assigned to either a high-CHO (n = 8) or high-MUFA (n = 9) diet to ensure that groups were matched for fasting blood glucose and BMI. **Intervention** • Mono unsaturated fatty acid (MUFA) enriched (low carbohydrate) diet for 6 weeks (n = 8) **Comparator** • High carbohydrate (low fat) diet for 6 weeks (n = 9) Both diets were hypocaloric; caloric intake was at a 50% deficit based on the Harris-Benedict equation multiplied by an activity factor of 1.7 (25,26) (mean caloric intake while dieting: MUFA group, 1,596 ± 86 kcal; CHO group, 1,750 ± 121 kcal). Each diet consisted of three servings of a liquid formula supplemented with a daily multivitamin and weighed amounts of celery. Both diets derived protein from a powder formula, Promod (Ross, Columbus, OH). For the MUFA formula, CHO and fat were derived from the powder formula New Directions (Ross) and high monounsaturated sunflower oil (supplied as Trisun Oil, SVO, Eastlake, OH), respectively. The CHO in the formula was hydrolyzed corn starch (50%) and simple CHO (sucrose and lactose). For the CHO formula, the CHO sources were Polycose (Ross), a polymer similar to hydrolyzed corn starch, and sucrose. Fat was derived from sunflower oil. Patients were seen at least twice weekly in the CRC Outpatient Clinic for pickup of formula. Patients were instructed on the proper technique for reconstituting the ingredients with water for outpatient consumption. They were also instructed to maintain a constant level of physical activity throughout the entire study
Outcomes	Assessments (12): baseline and twice weekly for 6 weeks **Primary outcome measures**

	1. Fasting plasma glucose/fasting plasma insulin ✱ 2. C-peptide, glucagon 3. Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoproteins A and B ✱ 4. Weight loss ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 14 : "This study was supported by grants from Ross Laboratories, the National Institutes of Health General Clinical Research Services (RR-00044), the National Heart, Lung, and Blood Institute (HL-14197), and a medical student fellowship award from the University of Rochester School of Medicine and Dentistry (to C.C.L.)."
Declaration of interest	Quote page 9: "B.G. has received research grants from Ross Laboratories, Slim Fast, Parke-Davis Pharmaceuticals, and Novartis (formerly Sandoz Nutrition) and honoraria and consulting fees from Parke-Davis and Wyeth-Ayerst Pharmaceuticals"
Notes	Medication: upon enrolment in the study, medications that would interfere with the results of the studies, including oral sulphonylurea agents, insulin, antihypertensive, and lipid-lowering therapies, were discontinued 2 weeks before metabolic testing, and patients were monitored in the CRC outpatient clinic. Insulin-treated type 2 diabetes patients were admitted to the CRC for safe termination of their treatment. For safety purposes, it was deemed medically necessary by the investigators and the institutional review board to administer low doses of insulin to patients with significant symptoms and fasting blood glucose > 16.7 mmol/L Mono unsaturated fatty acid (MUFA) enriched (low carbohydrate) diet: 10 en% carbohydrates, 20 en% protein, 70 en% fat, actual intake 9.5 en% carbohydrates, 20.6 en% protein, 69.9 en% fat High carbohydrate (low fat) diet: 70 en% carbohydrates, 20 en% protein, 10 en% fat, actual intake 70.1 en% carbohydrates, 19.5 en% protein, 10.3 en% fat (total adds up to 99.9%)

Risk of bias table of Gumbiner 1998 (74)

Study ID	Bias due to confounding	Bias in selection of the participants in the study	Bias in measurement of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall bias
Gumbiner 1998	Moderate risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Moderate risk of bias

Hockaday 1978 (75)

Methods	Randomized controlled study Setting Radcliffe Infirmary Diabetic Clinic, Oxford, UK Date of study Unspecified. Study duration 1 year
Participants	N = 93 (52 men, 41 women) Mean age: 51.5 years

	Inclusion criteria of the trial 1. Newly-diagnosed diabetics ≤ 65 years **Exclusion criteria of the trial** 1. Not suffering from any co-existent major illness 2. No requirement of immediate insulin therapy 3. The presence (or past history) of any other endocrine disease, myocardial infarction or neurological deficit following a cerebrovascular accident, precluded admission, as did the presence, but not a past history, of liver disease Withdrawals/losses to follow-up None reported Baseline data Weight (kg): low carb group 76.4, modified fat high carbohydrate group 82.2 Fasting triglyceride (mmol/L)(SE): low carb group 1.69 (0.12), modified fat high carbohydrate group 1.59 (0.12) Fasting glucose (mmol/L)(SE): low carb group 10.8 (0.58), modified fat high carbohydrate group 12.5 (0.72) Fasting insulin µ-units/ml (mmol/L)(SE): low carb group 11.0 (0.99), modified fat high carbohydrate group 10.8 (1.11)
Interventions	**Intervention** • Low carbohydrate diet for 1 year (n = 54) **Comparator** • Modified fat high carbohydrate diet for 1 year (n = 39) Patients were seen in the clinic after 1 month and then at 3-monthly intervals when they again talked with the dietitian. Dietary advice was then repeated The recommended energy content is determined from the excess above ideal body-weight (Metropolitan Life Insurance Co., 1959): an 8.4 (2000), 6.3 (1500) or 4.2 (1000) MJ (kcal) diet being prescribed if the patient is respectively more than 10, 20 or 30 % overweight.
Outcomes	Assessments (3): baseline, month 1 and year 1 **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Fasting plasma cholesterol 3. Fasting triglyceride ✱ 4. Weight ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 362: "We also gratefully acknowledge the financial support received from the British Diabetic Association and from the International Sugar Research Foundation Inc."
Declaration of interest	None declared.
Notes	Medication: patients who have been followed for 1 year and who did not require therapy with either insulin or oral hypoglycemic agents during this time Low carbohydrate diet: 20 en% carbohydrates, 20 en% protein, 40 en% fat Low fat diet: 54 en% carbohydrates, 20 en% protein, 26 en% fat

Risk of bias table of Hockaday 1978 (75)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 358): "Patients were randomly allocated to receive one of two types of dietary advice". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Patients were seen in the clinic after 1 month and then at 3-monthly intervals when they again talked with the dietician. Dietary advice was then repeated. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Quote (page 359): "Patients varied in their cooperation, but the report includes all subjects who entered the study". Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Unclear risk	Quote (page 359): "Many were obese; the extent of over-weight (% over ideal body-weight) was 28 in the group started on the LC diet and 37 amongst those on the MF diet, and the difference between the two groups at entry was statistically significant ($P < 0.02$). Quote (page 360): "Glucose levels on entry were higher in patients on the MF diet ($P = 0.05$)". Comment: We judged this as an unclear risk of bias.

Iqbal 2010 (76)

Methods	Randomized controlled study Setting Outpatient endocrinology, cardiology, and general medicine clinics at the Philadelphia Veterans Affairs Medical Center, US

Online Supporting Material (OSM) – Supplemental Table 6

	Date of study November 2004 until April 2008. Study duration 2 years
Participants	N = 144 (129 men, 15 women) Mean age: 60 years **Inclusion criteria of the trial** 1. Type 2 diabetes 2. Age ≥ 18 years 3. BMI ≥ 30 kg/m² **Exclusion criteria of the trial** 1. Serum creatinine concentration >1.5 mg/dl (133 μmol/l) 2. Urine albumin to-creatinine ratio >200 μg/mg 3. HbA1c <6.0% or >12.0% 4. Hypoglycemic or hyperglycemic episodes within the past month requiring external assistance 5. Weight loss ≥5% in the past 3 months 6. Participation in a weight-loss program 7. Use of weight-loss medications Withdrawals/losses to follow-up 76/144 (52.3%); 42/70 in low carbohydrate diet group, 34/74 in low fat diet group • Lost to follow-up: 12 in low carbohydrate diet group, 16 in low fat diet group • Were discouraged: 1 in low carbohydrate diet group, 2 in low fat diet group • Were not interested: 8 in low carbohydrate diet group, 4 in low fat diet group • Did not like the diet: 1 in very low carbohydrate diet group, 0 in low fat diet group • Were unable to attend: 5 in low carbohydrate diet group, 2 in low fat diet group • Were too busy: 1 in low carbohydrate diet group, 3 in low fat diet group • Moved: 3 in low carbohydrate diet group, 1 in low fat diet group • Withdrew for medical reason: 2 in low carbohydrate diet group, 1 in low fat diet group • Other reason: 3 in low carbohydrate diet group, 1 in low fat diet group • Dropped by principal investigator; 2 in low carbohydrate diet group, 2 in low fat diet group • Died: 3 in low carbohydrate diet group, 2 in low fat diet group Baseline data (SD) Weight (kg): low carb group 118 (21.3), low fat group 115.5 (16.7) BMI (kg/m²): low carb group 38.1 (5.5), low fat group 36.9 (5.3) HbA1c (%): low carb group 7.9 (1.7), low fat group 7.6 (1.3) Total cholesterol (mg/dl): low carb group 180.2 (46.3), low fat group 180.6 (41.5) LDL cholesterol (mg/dl): low carb group 109.6 (39.3), low fat group 107.7 (37.1) HDL cholesterol (mg/dl): low carb group 40.8 (12.8), low fat group 40.7 (12.7) Triglycerides (mg/dl): low carb group 154.9 (107.8), low fat group 167 (96.0) Systolic blood pressure (mm Hg): low carb group 139.7 (20.1), low fat group 140.1 (19.8) Diastolic blood pressure (mm Hg): low carb group 78.8 (10.3), low fat group 80.0 (12.2)
Interventions	**Intervention** • Low carbohydrate diet for 2 years (n = 70) **Comparator** • Low fat diet for 2 years (n = 74) Both diet groups were invited to attend separate weekly 2-h nutrition education classes for the first month. Thereafter, participants were provided sessions every 4 weeks for the duration of the study. Participants who had questions about their intervention also had

	the opportunity to meet individually with the dietitian at the end of the group session. All participants were encouraged to engage in at least 30 min of moderate activity at least five times per week, following joint guidelines from the Center for Disease Control and Prevention and the American College of Sports Medicine
Outcomes	Assessments (4): baseline, month 6, 12 and at 2 years **Primary outcome measures** 1. Weight ✱ 2. Fasting plasma glucose and HbA1c ✱ 3. Fasting plasma cholesterol 4. Fasting triglyceride, LDL and HDL ✱ 5. Blood pressure ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 1738: "Grant support: VA Merit Review Entry Program."
Declaration of interest	Quote page 1738 "The authors declared no conflict of interest."
Notes	Medication: oral medications for diabetes (%): sulphonylurea 57% in low carb diet group and 43.2% in low fat diet group; metformin 61.4% in low carb diet group and 52.7 in low fat diet group; thiazolidinediones 8.6% in low carb diet group and 10.8% in low fat diet group Insulin for diabetes (%): 22.9% in low carb diet group and 29.7% in low fat diet group Low carbohydrate diet: 30 g/day carbohydrates and a deficit of 500 kcal/day. Actual intake at 6 months 35.4 en% carbohydrates, 19.5 en% protein, 42.7 en% fat (total adds up to 97.6%), at 12 months 40.3 en% carbohydrates, 20.1 en% protein, 35.6 en% fat (total adds up to 96%), at 2 years 47.8 en% carbohydrates, 16.9 en% protein, 34.2 en% fat (total adds up to 98.9%) Low fat diet: <30 en% fat. Actual intake at 6 months 41.9 en% carbohydrates, 21.1 en% protein, 36.6 en% fat (total adds up to 99.6%), at 12 months 43 en% carbohydrates, 20.3 en% protein, 36.4 en% fat (total adds up to 99.7%), at 2 years 46.7 en% carbohydrates, 17.6 en% protein, 33.3 en% fat (total adds up to 97.6%) Actually: at 2 yrs low carb exceeds too much and low fat actually never matches. See Supplemental Table 4

Risk of bias table of Iqbal 2010 (76)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 358): "Patients were randomly allocated to receive one of two types of dietary advice" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been

		foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Patients received intensive dietary advice on both diets which was regularly repeated. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	76/144 (52.3%); 42/70 in low carbohydrate diet group, 34/74 in low fat diet group. All participants with a baseline measurement and at least one of the 3 other measurements were included in the mixed-model analysis (n = 138). Comment: We judged this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at ClinicalTrials.gov number, NCT00108459, and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Jones 1986 (77)

Methods	Randomized controlled, cross-over study Setting Oxford Diabetic Clinics, UK Date of study Unspecified. Study duration 6 weeks, and then cross-over for 6 weeks. No wash out period
Participants	N = 10 (4 men, 6 women) Mean age: 64.5 years (range 54-75 years) **Inclusion criteria of the trial** 1. Non-insulin dependent diabetes 2. Blood glucose > 12 mmol/L **Exclusion criteria of the trial**

	1. Medication affecting platelet function Withdrawals/losses to follow-up None reported Baseline data (SD) Nothing reported
Interventions	**Intervention** • Low carbohydrate diet for 6 weeks, followed by cross-over for 6 weeks **Comparator** • High carbohydrate high fiber diet for 6 weeks, followed by cross-over for 6 weeks
Outcomes	Assessments (3): baseline, weeks 6 and 12 **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. HbA1c ✱ 3. Total cholesterol, cholesterol in the lipoprotein fractions ✱ 4. Triglycerides ✱ 5. Serum insulin 6. Platelet phospholipid fatty acid measurements **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 67: "We are grateful to the Simon Broome Heart Research Trust for financial support".
Declaration of interest	None declared.
Notes	Medication: seven of the patients were taking chlorpropamide and metformin whilst the remaining three patients were taking chlorpropamide alone Low carbohydrate diet: 35 en% carbohydrates, 17 en% protein, 48 en% fat High carbohydrate (low fat) diet: 55 en% carbohydrates, 27 en% protein, 18 en% fat Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is more than 30 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Jones 1986 (77)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 66): "the patients were randomised to receive..." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and

		patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at a high risk of bias.

Lerman-Garber 1995 (78)

Methods	Randomized controlled, cross-over study Setting Department of Diabetes and Lipid Metabolism, Nutrition Division and Department of Infectology, Instituto Nacíonal de la Nutrición, Salvador Zubirán, Mexico City, Mexico Date of study Unspecified. Study duration 6 weeks, 6 weeks washout and then cross-over for 6 weeks
Participants	N = 20 (all women) Mean age (SD): 60 (7) years **Inclusion criteria of the trial** 1. Previous diagnosis of non-insulin dependent diabetes mellitus 2. Poor glycemic control (mean fasting blood glucose >180 mg/dl) 3. Glycosylated hemoglobin >9.5% (normal ranges 5-8%) 4. Elevated fasting triglycerides levels (mean fasting triglycerides > 150 mg/dl) for at least the last 3 months **Exclusion criteria of the trial** 1. No concurrent acute illness 2. Thyroid, renal or hepatic disease Withdrawals/losses to follow-up 4/20 had less than 80% adherence to the diet and were excluded 3/20 only finished first dietary period and were lost due to socio-economical reasons Baseline data (SD) Body weight (kg): 58.8 (8.6) BMI (kg/m²): 25.2 (2.3) HbA1c (%): HMUFA diet 12.6 (2.6), HCHO diet 11.1 (1.9) Glucose (mg/dl): HMUFA diet 210 (47), HCHO diet 223 (55) Total cholesterol (mg/dl): HMUFA diet 233 (52), HCHO diet 242 (50) LDL-cholesterol (mg/dl): HMUFA diet 152 (55), HCHO diet 160 (48) HDL-cholesterol (mg/dl): HMUFA diet 38.9 (7.7), HCHO diet 40.1 (5.8) Triglycerides (mg/dl): HMUFA diet 274 (173), HCHO diet 264 (131)

Interventions	**Intervention** • Diet high in monounsaturated fatty acids (HMUFA)(low carb diet) for 6 weeks, 6 weeks washout and then cross-over for 6 weeks **Comparator** • Diet high in complex carbohydrates (HCHO)(low fat diet) for 6 weeks, 6 weeks washout and then cross-over for 6 weeks Patients received menus every day. Every week or two as needed, and at the end of each study period, the patients were seen by the nutritionist and had a 24-hr diet recall.
Outcomes	Assessments (4): baseline, weeks 6, 12 and 18 **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. HbA1c ✱ 3. Total cholesterol, HDL, LDL ✱ 4. Triglycerides ✱ **Secondary outcome measures** 1. Weight ✱ ✱ Denotes outcomes prespecified for this review
Funding source	None declared
Declaration of interest	None declared
Notes	Medication: all were being treated with oral agents and/or insulin, 69% had arterial hypertension and were on diuretics, angiotensin-converting enzyme inhibitors or calcium channel blockers, which were continued with no changes during the study. Diet high in monounsaturated fatty acids (HMUFA)(low carb diet): 40 en% carbohydrates, 20 en% protein, 40 en% fat Diet diet high in complex carbohydrates (HCHO)(low fat diet): 60 en% carbohydrates, 20 en% protein, 20 en% fat

Risk of bias table of Lerman-Garber 1995 (78)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 140): "Patients were randomly assigned to". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Patients received menus every day. Every week or two as needed, and at the end of each study period, the patients were seen by the nutritionist and had a 24-hr diet recall. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g.

		adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	7/20 (35%) were not included in the analysis. Reasons reported. Comment: We judged this as at high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Unclear risk	The baseline HbA1c was higher in the HMUFA (low carbohydrate) group than in the HCHO low fat group. Comment: We judged this as at an unclear risk of bias.

Lopez-Espinoza 1984 (79)

Methods	Randomized controlled study Setting Sheikh Rashid Diabetes Unit, Radcliffe Infirmary, Oxford, UK Date of study Not specified. Study duration 7 years
Participants	N = 59 (34 men, 25 women) Mean age (SD): 56 (9.2) years **Inclusion criteria of the trial** 1. Non-insulin-dependent diabetes mellitus **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up Not reported Baseline data (SD) Weight (kg): low carb diet group 74.4 (9.4), modified fat diet group 81.1 (13.9) BMI (kg/m²): low carb diet group 28.7 (3.3), modified fat diet group 31.9 (5.4)
Interventions	**Intervention** • Low carbohydrate diet for 7 years (n = 25) **Comparator** • Modified fat diet for 7 years (n = 34)
Outcomes	Assessments (2): baseline and year 7 **Primary outcome measures** 1. Phospholipid fatty acid composition of platelets 2. Development of retinopathy **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 47: "This study was supported by the Simon Broome Heart Research Trust and the Oxford Diabetes Trust funding of the Sheikh Rashid Diabetes Unit."
Declaration of interest	None declared
Notes	Medication: 25 also took hypoglycemic sulphonylureas and nine were on insulin.

	Low carbohydrate diet: 40 en% carbohydrates, nothing further reported Modified fat (low fat) diet: 30 en% fat, nothing further reported None of our outcomes were addressed (see Supplemental Table 4)

Risk of bias table of Lopez-Espinoza 1984 (79)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 41): "a prospective study and randomized to advice". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	None reported, but unlikely there were no losses to follow up over the 7 years. Comment: There was insufficient information to permit a clear judgement.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Unclear risk	There was baseline imbalance between groups for BMI. The BMI was higher in the modified fat diet group Comment: We judged this as at an unclear risk of bias.

Lousley 1983 (80)

Methods	Randomized controlled, cross-over study Setting Diabetes Research Laboratories and Department of Community Medicine and General Practice, Radcliffe Infirmary, Oxford, UK Date of study Unspecified. Study duration 6 weeks, no washout and then cross-over for 6 weeks
Participants	N = 15 (gender unclear) Age range: 51 to 75 years **Inclusion criteria of the trial** 1. Non-insulin dependent diabetes mellitus

	2. On high doses of oral hypoglycemic agents 3. Three consecutive blood glucose measurements > 12 mmol/L **Exclusion criteria of the trial** 1. Change in body weight in previous 6 months Withdrawals/losses to follow-up 4/15 (26.6%); 2 were unable to comply to high carbohydrate-high fiber diet, 1 discontinued after 1st phase and 1 non-compliant Baseline data (SD) Individual patient data are provided regarding weight
Interventions	**Intervention** • Low carbohydrate diet for 6 weeks, followed by cross-over for 6 weeks **Comparator** • High carbohydrate-high fiber (low fat) diet for 6 weeks, followed by cross-over for 6 weeks
Outcomes	Assessments (3): baseline and weeks 6 and 12 **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Total cholesterol 3. LDL, HDL and VLDL cholesterol ✱ 4. Triglycerides ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 25: "We are grateful...to the British Diabetic Association and the Simon Broome Heart Research Trust for financial support"
Declaration of interest	None declared
Notes	Medication: patients continued oral anti glycemic medication (or diminished) Low carbohydrate diet: 35 en% carbohydrates, 22 en% protein, 43 en% fat High carbohydrate -high fiber (low fat) diet: 60 en% carbohydrates, 24 en% protein, 16 en% fat Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is more than 30 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias of Lousley 1983 (80)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 21): "They were then randomly placed on either a high carbohydrate-high fibre diet (HC) or a reinforced low carbohydrate diet". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.

Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Detailed dietary instruction was given for both diets. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	4/15 (26.6%); 2 were unable to comply to high carbohydrate-high fiber diet, 1 discontinued after 1st phase and 1 non-compliant. Comment: We considered this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was a too short wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Myashita 2004 (81)

Methods	Randomized controlled study Setting Center of Diabetes, Endocrine and Metabolism, Sakura Hospital, School of Medicine, Toho University, Sakura-City, Chiba, Japan Date of study Not specified. Study duration 4 weeks
Participants	N = 22 (16 men, 6 women) Mean age (SD): 52.4 (13) years **Inclusion criteria of the trial** 1. Obese subjects with type 2 diabetes mellitus 2. No medications **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SD) BMI (kg/m²): low carb diet group 27 (4), high carb (low fat) diet group 27 (2) HbA1c (%): low carb diet group 10.2 (2), high carb (low fat) diet group 9.8 (2) Fasting blood glucose (mg/dl): low carb diet group 207 (36), high carb (low fat) diet group 200 (50) Total cholesterol (mg/dl): low carb diet group 199 (35), high carb (low fat) diet group 193 (48)

	Triglyceride (mg/dl): low carb diet group 175 (89), high carb (low fat) diet group 173 (60) HDL cholesterol (mg/dl): low carb diet group 38 (10), high carb (low fat) diet group 39 (16)
Interventions	The subjects were initially given a 3 day low calorie diet composed of high carbohydrate (1000 kcal per day, Protein:Fat:Carbohydrate = 26:10:62) **Intervention** • Low carbohydrate diet for 4 weeks (n = 11) **Comparator** • High carbohydrate (low fat) diet for 4 weeks (n = 11) They were all hospitalized. All patients were without medications and treated with exercise therapy (walking, 30 min × 2 times per day) and took no medication Both diets contained 1000 kcal per day
Outcomes	Assessments (2): baseline and end of study **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. Fasting serum total cholesterol, HDL and triglycerides ✱ 3. Body weight, total body fat ✱ 4. Measurement visceral and subcutaneous fat mass **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 241: "This study is supported partly by a fund from the Meeting of Obesity and Nutritional Disturbance".
Declaration of interest	None declared
Notes	During this study, all patients were without medications Low carbohydrate diet: 40 en% carbohydrates, 25 en% protein, 35 en% fat High carbohydrate low calorie (low fat) diet: 65 en% carbohydrates, 25 en% protein, 10 en% fat

Risk of bias table of Miyashita 2004 (81)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 235): "were randomly assigned". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. The subjects were treated for 4 weeks with these diets, whilst hospitalized. During this study, all patients were without medications and treated with exercise therapy (walking, 30 min × 2 times per day). However, we cannot rule out the effect of expectations

		of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Ney 1982 (82)

Methods	Randomized controlled study Setting High Risk Obstetrics Clinic of the University of California, San Diego, US Date of study Not specified. Study duration 14-18 weeks
Participants	N = 20 (all women) Mean age: in type 1 diabetes 26.6 years and in type 2 diabetes 32.2 years **Inclusion criteria of the trial** 1. Pregnant diabetic women (both type 1 and type 2 diabetes mellitus) **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SD) HbA1c (%): control (low carbohydrate) diet group 10.2 (0.6), high carbohydrate (low fat) diet group 11.0 (0.5) Plasma glucose (mg/dl): control (low carbohydrate) diet group 179 (19), high carbohydrate (low fat) diet group 154 (8)
Interventions	**Intervention** • Control (low carbohydrate) diet for 14-18 weeks (n = 10) **Comparator** • High carbohydrate (low fat) diet for 14-18 weeks (n = 10) All patients were hospitalized in the UCSD School of Medicine General Clinical Research Center (GCRC) at 10-30 wk gestation for an 8-day baseline evaluation and for metabolic studies and intensive dietary education. After discharge from the GCRC, each patient was seen weekly in the High Risk Obstetrics Clinic for medical supervision of pregnancy, nutritional counselling, and evaluation of dietary compliance Total caloric intake was individualized according to weekly weight gain and activity levels and based on a projected total weight gain for pregnancy of 20-30 lb. Type I patients were instructed to eat three meals plus snacks at 10:00 h, at 15:00 h, and at bedtime, while type II patients were counselled to eat three meals with a bedtime snack
Outcomes	Assessments (4): baseline, week 25 gestation, 34-35 week gestation and 12 week postpartum **Primary outcome measures**

	1. Fasting plasma glucose ✱ 2. HbA1c ✱ 3. Mean amplitude of glycemic excursions (MAGE) 4. Mean 24-h urinary loss of glucose 5. Daily exogenous insulin requirement **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 533: "This project was supported in part by the UCSD General Clinical Research Center NIH/Division of Research Resources Grant RR-0827, and N1H Grant RO1 HD-13469
Declaration of interest	None declared
Notes	Medication: decisions regarding management strategy and insulin adjustment were made weekly following the clinic visit Control low carbohydrate) diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat High carbohydrate (low fat) diet: 65 en% carbohydrates, 20 en% protein, 15 en% fat No separate data for women with type 1 and type 2 diabetes. Study is > 35 years old (see Supplemental Table 4)

Risk of bias table of Ney 1982 (82)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 529): "were randomly assigned". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Detailed dietary instruction and counselling was given for both diets. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported.

		Comment: We judged this as at a low risk of bias.
Other bias	Low risk	Comment: The study appeared to be free of other forms of bias.

Nielsen 2005 (83)

Methods	Controlled study Setting Department of Medicine, Blekingesjukhuset, Karlshamn, Sweden Date of study Unspecified. Study duration 6 months
Participants	N = 31 (gender unclear) Mean age (SD): 57.1 (6.2) years in low carb diet group, 58.6 (10.1) in control group **Inclusion criteria of the trial** 1. Obese patients (BMI> 30 kg/m²) with type 2 diabetes mellitus **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SD) Body weight (kg): low carb diet group 100.6 (14.7), high carb (low fat) diet group 101.5 (14.5) Fasting glucose (mmol/L): low carb diet group 11 (2.8), high carb (low fat) diet group 12.3 (1.8) HbA1c (%): low carb diet group 8.0 (1.5), high carb (low fat) diet group 7.9 (1.4) BMI (kg/m²): low carb diet group 36.1 (4.2), high carb (low fat) diet group 34.2 (3.9)
Interventions	**Intervention** • Low carbohydrate diet for 6 months (n = 16) **Comparator** • High carbohydrate (low fat) diet for 6 months (n = 15) All patients received information about a caloric restricted diet. All patients were instructed to exercise 30 minutes a day and to take a daily multivitamin supplement containing extra calcium
Outcomes	Assessments (8): baseline and weeks 2, 4, 6, 8, 10, 12 and 24 **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. HbA1c ✱ 3. Bodyweight ✱ 4. BMI ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 183: "The project was supported by a grant from the Medical Research Committee in Blekinge, Sweden"
Declaration of interest	None declared
Notes	Medication in low carbohydrate group: 11 were insulin treated, 15 received metformin, and 5 sulphonylurea Medication in high carbohydrate (low fat) diet group: 6 were insulin-treated, 10 received metformin, and 5 sulphonylurea

	Low carbohydrate diet: 20 en% carbohydrates, 30 en% protein, 50 en% fat, 1800 kcal for men and 1600 kcal for women High carbohydrate (low fat) diet: 60 en% carbohydrates, 15 en% protein, 25 en% fat, 1600-1800 kcal for men and 1400-1600 kcal for women

Risk of bias table of Nielsen 2005 (83)

Study ID	**Bias due to confounding**	**Bias in selection of the participants in the study**	**Bias in measurement of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of reported result**	**Overall bias**
Nielsen 2005	Serious risk of bias	Moderate risk of bias	Low risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias

Nutall 2012 (84)

Methods	Randomized controlled, cross-over study Setting Special Diagnostic and Treatment Unit, Department of Food Science and Nutrition, University of Minnesota, Minneapolis, US Date of study Unspecified. Study duration 5 weeks, washout 5 weeks, then cross-over for 5 weeks
Participants	N = 9 (all men) Mean age (SE): 61 (2.1) years **Inclusion criteria of the trial** 1. Diabetes type 2 **Exclusion criteria of the trial** 1. Hematologic abnormalities 2. Liver disease 3. Kidney disease, macroalbuminuria (>300 mg/24 h) 4. Untreated thyroid disease 5. Congestive heart failure 6. Angina 7. Life-threatening malignancies 8. Proliferative retinopathy 9. Diabetic neuropathy 10. Peripheral vascular disease, 11. Serious psychological disorders. 12. Weighing more than 136 kg (300 lb) Withdrawals/losses to follow-up 1/9 (11.1%); One individual participated in a humanitarian aid project during the washout period. He lost a considerable amount of weight during this time, and thus did not complete the second arm of the study Baseline data (SE) HbA1c (%): 8.8 (0.5) BMI (kg/m²): 31 (0.9) Weight (kg): LoBAG (low carb) diet group 97.2 (2.3), control (low fat) diet group 97.6 (2.6) Systolic blood pressure (mmHg): LoBAG (low carb) diet group 139 (4), control (low fat) diet group 140 (9)

	Diastolic blood pressure (mmHg): LoBAG (low carb) diet group 78 (3), control (low fat) diet group 83 (4) HDL cholesterol (mg/dl): LoBAG (low carb) diet group 36 (2), control (low fat) diet group 39 (2) LDL cholesterol (mg/dl): LoBAG (low carb) diet group 102 (12), control (low fat) diet group 92 (10) Triglycerides (mg/dl): LoBAG (low carb) diet group 138 (19), control (low fat) diet group 142 (24)
Interventions	**Intervention** • Low Biologically Available Glucose (LoBAG) (low carb) diet for 5 weeks, washout 5 weeks, then cross-over for 5 weeks **Comparator** • Control (low fat diet) for 5 weeks, washout 5 weeks, then cross-over for 5 weeks A six-day rotating menu was used. Total food energy was individualized to insure that each subject remained weight stable during the study. Dietary preferences were accommodated whenever possible. All food was provided to the subjects The diets were isocaloric
Outcomes	Assessments (4): baseline and weeks 5, 10 and 15 **Primary outcome measures** 1. Total alpha amino acid nitrogen 2. Individual specific amino acids 3. Cortisol and glucagon 4. 24-hour urinary free cortisol, microalbumin, calcium, creatinine, glucose, pH, potassium, sodium, urea and uric acid 5. Plasma and/or urine creatinine, urea nitrogen, sodium, potassium, glucose, uric acid, total cholesterol, HDL-cholesterol, triacylglycerol, pre-albumin and albumin ✱ 5. Body composition data (weight, measurement of fat-free mass) ✱ **Secondary outcome measures** 1. No specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 11: "Supported in part from merit review funds from the Department of Veterans Affairs, and grants from The National Pork Board, the Minnesota Beef Council and the National Cattlemen's Beef Association, funded by "The Beef Checkoff."
Declaration of interest	Quote page 11: "The authors declare that they have no competing interests"
Notes	Medication: all subjects signed consent forms and all also obtained approval from their primary care provider before discontinuing their oral antidiabetic medications. Other medications were continued and remained unchanged during the study. Low Biologically Available Glucose (LoBAG) (low carb) diet: 30 en% carbohydrates, 30 en% protein, 40 en% fat Control (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat The washout period is considered long enough, therefore we could include the data Data of Gannon 2011 provide data on the same study population, but other outcomes (e.g. HbA1c, bodyweight, insulin growth factor, and binding proteins 1 and 3, ghrelin, growth hormone)

Risk of bias table of Nutall 2012 (84)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "A randomized, crossover, 5 week design", quote paper Gannon 2011 (copublication) "as determined by a flip of a coin". Comment: Probably done.
Allocation concealment (selection bias)	Low risk	Quote paper Gannon 2011 (copublication) "as determined by a flip of a coin" Comment: It was not possible to foresee allocation before enrolment.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Total food energy was individualized to insure that each subject remained weight stable during the study. Dietary preferences were accommodated whenever possible. All food was provided to the subjects. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	One loss to follow-up (11.1%) reported, reason reported. Per-protocol analysis. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol of the study was available at clinicaltrials.gov (NCT00108225) but outcomes were not prespecified, but those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Rodríguez-Villars 2004 (85)

Methods	Randomized controlled, cross-over study <u>Setting</u> Lipid Clinic, Nutrition and Dietetics Service and Clinical Biochemistry Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínico, Barcelona, Spain <u>Date of study</u> Unspecified. Study duration 6 weeks, and then cross-over for 6 weeks. No wash-out period between diets incorporated
Participants	N = 26 (13 men, 13 women) Mean age: 61 years **<u>Inclusion criteria of the trial</u>** 1. Medically stable patients with fairly well-controlled type 2 diabetes attending the out-patient lipid and diabetes clinics

	2. Body mass index < 35 kg/m² 3. Serum HbA1c ≤ 8.0% 4. Serum cholesterol ≤ 7.2 mmol/L 5. Triglycerides ≤ 3.0 mmol/L 6. Treatment with diet or oral hypoglycemic agents **Exclusion criteria of the trial** 1. Smokers 2. Subjects with alcohol intake > 20 g per day 3. Diagnosis of diabetic enteropathy, renal disease, thyroid disease, or drug-treated hypertension 4. Intake of antioxidant vitamins or hypolipidemic drugs Withdrawals/losses to follow-up 4/26 (15.4%) due to poor dietary compliance Baseline data (SD) Weight (kg): 80.2 (16.0) BMI (kg/m²): 28.3 (3.9) Waist (cm): 100 (7) Fasting blood glucose (mmol/L): 9.0 (2.7) HbA1c (%): 6.5 (0.9) LDL cholesterol (mmol/L): 3.36 (0.71) HDL cholesterol (mmol/L): 1.21 (0.37) Triglycerides (mmol/L): 2.02 (0.81)
Interventions	During a 6-week pre-inclusion period individuals consumed their usual diabetic diet low in SFA and high in carbohydrates **Intervention** • High-monounsaturated fatty acid (MUFA) diet (low carb) diet for 6 weeks, then cross-over for 6 weeks **Comparator** • High-carbohydrate diet (low fat diet) for 6 weeks, then cross-over for 6 weeks The experimental diets were individually prescribed and based on estimated energy requirements. As participants ate on their own, detailed dietary information was provided to them and, if appropriate, to their partners. Diets were calculated in increments of 200 kcal, to cover the range from 1600 to 2200 kcal. The prescribed diets were isocaloric and differed only in the content of fat and complex carbohydrate. Adherence to the study diet was monitored from 3-day food records completed by participants every 2 weeks Instructions to maintain a similar level of physical activity for the duration of the study were provided
Outcomes	Assessments (3): baseline and weeks 6 and 12 **Primary outcome measures** 1. LDL resistance to oxidation from the high-carbohydrate diet **Secondary outcome measures** 1. Weight ✱ 2. BMI ✱ 3. Fasting serum glucose/insulin ✱ 4. HbA1c ✱ 5. Total cholesterol, HDL, LDL, VLDL and triglycerides ✱ 5. Apolipoprotein B and AI ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 147: "This study was supported in part by grants from CICYT, Comisión Interministerial de Ciencia y Tecnología of Spain (OLI 96-2132), and Fundació Privada Catalana de Nutrició i Lípids"

Declaration of interest	None declared
Notes	Medication: oral hypoglycemic medication was continued High-monounsaturated fatty acid (MUFA) diet (low carb) diet: 40 en% carbohydrates, 15 en% protein, 40 en% (total adds up to 95%), actual intake at 6 weeks 41.4 en% carbohydrates, 17.5 en% protein, 40.2 en% (total adds up to 99.1%) High-carbohydrate diet (low fat diet): 50 en% carbohydrates, 15 en% protein, 30 en% (total adds up to 95%), actual intake at 6 weeks 52.3 en% carbohydrates, 18.9 en% protein, 27.9 en% (total adds up to 99.1%) Data from both study periods are pooled and no separate data per study period are available. No wash-out period. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Rodríguez-Villar 2004 (85)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 143): "Participants were randomly assigned to the two diet sequences (henceforth named CHO and MUFA) using a computer-generated random number table, with stratification by sex." Comment: Probably done.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	4/26 (15.4%) due to poor dietary compliance. Comment: Moderate number of losses to follow up. We judged this as at an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first

		period/phase were available. Comment: We judged this as at high risk of bias.

Samaha 2003 (86)

Methods	Randomized controlled study Setting Philadelphia Veterans Affairs Medical Center, Philadelphia, US Date of study May until November 2011. Study duration 6 months
Participants	N = 132 (109 men, 23 women) Mean age: 54 years **Inclusion criteria of the trial** 1. Age ≥ 18 years 2. BMI ≥ 35 years **Exclusion criteria of the trial** 1. Serum creatinine level > 1.5 mg/dl (132.6 μmol/l) 2. Hepatic disease 3. Severe, life-limiting medical illness 4.Inability of diabetic subjects to monitor their own glucose levels 5.Active participation in a dietary program; or use of weight loss medications Withdrawals/losses to follow-up 53/132 (40.1%); 21/64 in low carbohydrate diet group, 32/68 in low fat diet group. Reasons not reported Baseline data (SD) of the whole group BMI (kg/m²): low carb diet group 44 (7), low fat diet group 43 (7) Diabetes (%): low carb diet group 41, low fat diet group 38 Weight (kg): low carb diet group 130 (22.7), low fat diet group 131.8 (27.3) Systolic blood pressure (mm Hg): low carb diet group 133 (15), low fat diet group 135 (16) Diastolic blood pressure (mm Hg): low carb diet group 78 (11), low fat diet group 80 (9) Triglycerides (mg/dl): low carb diet group 188 (176), low fat diet group 176 (120) Total cholesterol (mg/dl): low carb diet group 181 (52), low fat diet group 192 (30) HDL cholesterol (mg/dl): low carb diet group 41 (11), low fat diet group 41 (10) LDL cholesterol (mg/dl): low carb diet group 114 (36), low fat diet group 118 (29) Glucose level in all subjects (mg/dl): low carb diet group 128 (53), low fat diet group 124 (47) Glucose level in non-diabetic subjects: low carb diet group 102 (14), low fat diet group 103 (14) Glucose level in diabetic subjects : low carb diet group 168 (63), low fat diet group 158 (61) HbA1c (%) in diabetic subjects: low carb diet group 7.8 (1.2), low fat diet group 7.4 (1.5)
Interventions	**Intervention** • Low carbohydrate diet for 6 months (n = 64) **Comparator** • Low fat diet for 6 months (n = 68) The two diet groups attended separate two-hour group-teaching sessions each week for four weeks followed by monthly one-hour sessions for five additional months; all sessions were led by experts in nutritional counselling. Subjects received a diet overview handout, instructional nutrition labels, sample menus and recipes, and a book on counting calories and carbohydrates. No specific exercise program was recommended

Outcomes	Assessments (2): baseline and month 6 (except weight every month) **Primary outcome measures** 1. Weight ✱ 2. Blood pressure ✱ 3. Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides ✱ 4. Fasting glucose and insulin **Secondary outcome measures** 1. Not specified. However, although not prespecified as an outcome, data are reported on HbA1c ✱ ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 2081: "Supported by funding from the Veterans Affairs Healthcare Network Competitive Pilot Project Grant"
Declaration of interest	None declared
Notes	Medication: many of the subjects were taking lipid-lowering medications, antihypertensive and hypoglycemic agents Low carbohydrate diet: < 30 gram/day carbohydrates. No instruction on restricting total fat intake was provided. Vegetables and fruits with high ratios of fiber to carbohydrate were recommended. Actual intake at 6 months 37 en% carbohydrates, 22 en% protein, 41 en% fat Low fat diet: < 30 en% fat, instruction in accordance with the obesity-management guidelines of the National Heart, Lung, and Blood Institute including "caloric restriction sufficient to create a deficit of 500 calories per day". Actual intake at 6 months 51% en% carbohydrates, 16 en% protein, 33 en% fat At 6 months the actual intake of fat was 33% in the low fat diet group, which exceeded the 2 en% limit of excess we would accept (see Methods section). Furthermore, data are reported on some outcomes for diabetics (glucose, insulin and Hb1Ac), but it is unclear how many diabetic patients were left in each intervention group as we know there was a 40% drop out but no mentioning about how many diabetics dropped out in each intervention group, making it impossible for us to analyze the data, (see Supplemental Table 4)

Risk of bias table of Samaha 2003 (86)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 2075): "randomly assigned to either the low-carbohydrate diet or the low-fat diet, with use of a pre-established algorithm generated from a random set of numbers. We used stratified randomization, with blocking within strata, to ensure that each group would contain approximately equal numbers of women, subjects with diabetes, and severely obese subjects (body-mass index, 40 or higher)." Comment: Probably done.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.

Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 2075): "The study was not blinded". Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Detailed dietary instruction and counselling was given for both diets. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 2075): "The study was not blinded". However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	Drop-outs: 53/132 (40.1%); 21/64 in low carbohydrate diet group, 32/68 in low fat diet group. Reasons not reported. Per-protocol analysis. Comment: We judged this as at a high risk of bias.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was not available but the outcomes mentioned in the methods section appeared to have been reported. HbA1c was not a prespecified outcome in any of the 3 papers that reported data on this and can be seen as some selective reporting to show low carb diet doing better. Comment: We judged this as at a unclear risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Saslow 2017 (87)

Methods	Randomized controlled study Setting Multi-center, US Date of study October 2013 until June 2015. Study duration 32 weeks
Participants	N = 25 (10 men, 15 women) Mean age: 56 years **Inclusion criteria of the trial** 1. Age ≥ 18 years 2. BMI ≥ 25 years 3. An elevated HbA1c diagnostic of type 2 diabetes (6.5%-9% measured at baseline of the study) **Exclusion criteria of the trial** 1. Diabetes medication other than metformin Withdrawals/losses to follow-up 7/25 (28%); 1/12 in very low carbohydrate diet group, 6/13 in control (low fat) diet group • Did not complete allocated intervention: 0 in very low carbohydrate diet group, 5 in control (low fat) diet group • Lost to follow-up: 1 in very low carbohydrate diet group, 1 in control (low fat) diet group Baseline data (SD)

	HbA1c (%): very low carb diet group 7.1 (0.4), control (low fat) diet group 7.2 (0.3) Weight (kg): very low carb diet group 109.7 (24.9), control (low fat) diet group 90.9 (16.4) Triglycerides (mg/dl): very low carb diet group 174.1 (79.4), control (low fat) diet group 151.5 (87.1) HDL cholesterol (mg/dl): very low carb diet group 45.7 (15.0), control (low fat) diet group 53.9 (12.7) LDL cholesterol (mg/dl): very low carb diet group 96.9 (30.4), control (low fat) diet group 90.9 (16.4) Diabetes-related distress: very low carb diet group 1.9 (0.8), control (low fat) diet group 2.4 (1.2) CES-Depression: very low carb diet group 10.5 (7.7), control (low fat) diet group 9.8 (7.4) CES-D Positive Affect: very low carb diet group 10.2 (2.3), control (low fat) diet group 10.2 (2.2) DES Negative Affect: very low carb diet group 2.8 (1.3), control (low fat) diet group 2.7 (1.4) DES Positive Affect: very low carb diet group 6.5 (1.1), control (low fat) diet group 6.2 (1.5) Vitality (SF-36 subscale): very low carb diet group 53.3 (16.4), control (low fat) diet group 49.2 (20.1)
Interventions	**Intervention** • Very low carbohydrate diet for 32 weeks (n = 12) **Comparator** • Control (low fat) diet for 32 weeks (n = 13) For the very low carb diet group: Lifestyle changes were recommended including behavioral adherence strategies aimed at increasing positive affect regulation and mindful eating based largely on the Mindfulness-Based Eating Awareness Training program, using handouts and lesson content the lessons discussed the importance of physical activity and sleep as well as encouraged participants to increase their level of physical activity and amount of sleep. Participants in this group were mailed new lessons weekly for the first 16 weeks and then every two weeks for the remaining 16 weeks of the study. The lessons included videos, hand-outs and links to online resources For the control (low fat) diet group: the American Diabetes Associations' "Create Your Plate" diet, a low-fat diet. This group was taught to use short videos created for the study (approximately 5-10 minutes long), with printable handouts and links to online resources, such as links to online recipes and recipe books. The standard dietary information in this group was chosen, and not all the extra behavioral help, in order to have this condition be a minimal dietary control group. The participants in this group were mailed new lessons weekly for the first 4 weeks and then every 4 weeks thereafter. This group did not get the positive affect regulation and mindful eating materials
Outcomes	Assessments (2): baseline and weeks 16 and 32 **Primary outcome measures** 1. HbA1c ✱ 2. Fasting serum HDL cholesterol, LDL cholesterol, triglycerides ✱ 3. Weight ✱ 4. Psychological self-report (Diabetes Distress Scale) 5. Center for Epidemiological Studies Depression Scale (CESD) 6. Modified Differential Emotions Scale (mDES)

	7. Self-assessed physical symptoms with adapted Short Form Health survey to measure of health-related quality of life, to assess vitality (energy and fatigue) ✱ 8. Dietary Self-Report (My FitnessPal) **Secondary outcome measures** 1. Not specified. ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 13 : "The research was supported by a grant from the Mount Zion Health Fund. Laura Saslow and Ashley Mason were supported by National Institutes of Health (NIH) grant T32AT003997 from the National Center for Complementary and Integrative Health (NCCIH). Laura Saslow was also supported by funding from the William K Bowes, Jr Foundation and the NIH (K01 from the National Institute of Diabetes and Digestive and Kidney Diseases, DK107456). Ashley Mason was also supported by the NIH (K23 from the National Heart, Lung, and Blood Institute, HL133442). Judith Moskowitz was supported by NIH grant K24 MH093225 from the National Institute of Mental Health. Frederick Hecht was supported by NIH grant K24 AT007827 from NCCIH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."
Declaration of interest	Quote page 13: "Frederick Hecht is on the Scientific Advisory Board for Virta Health. No other author declares any conflict of interest"
Notes	Medication: patients were allowed to continue metformin but no other medication Very low carbohydrate diet: 20-50 gram/day carbohydrates. Actual intake at 16 weeks 16.8 en% carbohydrates, 29.4 en% protein, 53.7 en% fat, at 32 weeks 17.1 en% carbohydrates, 26.8 en% protein, 56.1 en% fat Low fat diet: < 30 en% fat, an online diet program based on the American Diabetes Associations' "Create Your Plate" diet. Actual intake at 16 weeks 40.8 en% carbohydrates, 20.9 en% protein, 38.3 en% fat, at 32 weeks 45.2 en% carbohydrates, 20.7 en% protein, 34.1 en% fat As the actual intake of fat in the control plate at 16 and 32 weeks is 38.3 en% and 34.1 en% respectively this exceeds our limits of the low fat diet and therefore we did not include the data (see Supplemental Table 4)

Risk of bias table of Saslow 2017 (87)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 3): "sequence for randomization, which was created by a statistician using block randomization procedures, with blocks of size randomly allocated to size 2, 4, or 6". Comment: Probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 3): "opening the next opaque envelope in a series containing the concealed sequence for randomization". Comment: Allocation appears to have been adequately concealed.
Blinding of participants and personnel (performance bias)	High risk	Quote (page 3): "For this study, it was not possible for the participants and staff to be masked to group allocation". Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Detailed dietary instruction and counselling was given for both diets. However, the control group did not receive the behavioural

		instruction (mindfulness, exercise instructions and recommendations of lifestyle changes). The very low carbohydrate diet group received more attention and we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at high risk of bias.
Blinding of outcome assessment (detection bias)	Unclear risk	The majority of outcome measurements were objective and unlikely to be influenced, but the questionnaires were subjective and therefore likely to be influenced Comment: We consider the risk of bias for this outcome to be unclear.
Incomplete outcome data (attrition bias)	High risk	7/25 (28%); 1/12 in very low carbohydrate diet group, 6/13 in control (low fat) diet group. Per protocol analysis. Comment: High and unbalanced number of drop-outs combined with a per-protocol analysis considered at high risk of bias.
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available at ClinicalTrials.gov number NCT01967992, and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. But there are extra outcomes reported that did not appear to be predefined (lipids and effects on mental health. Comment: We judged this as at an unclear risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Shah 2005 (88)

Methods	Randomized controlled, cross-over study Setting Metabolic units of the Stanford University, Stanford, CA, the University of Texas Southwestern Medical Center, Dallas, TX, the University of Minnesota, Minneapolis, MN, and the Veterans Affairs Medical Center, San Diego, CA, US Date of study Unspecified. Study duration 6 weeks, 1 week washout followed by cross-over for 6 weeks
Participants	N = 42 (33 men, 9 women) Mean age (SD): 58 (10) years **Inclusion criteria of the trial** 1. Diabetes type 2 **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None, but of one there are no blood pressure data Baseline data (SD) BMI (kg/m²): 28.1 (2.9) Systolic blood pressure (mmHg): 134 (18) Diastolic blood pressure (mmHg): 80 (9)
Interventions	**Intervention** • High cis-monounsaturated fat (low carbohydrate) diet for 6 weeks, 1 week washout followed by cross-over for 6 weeks

	Comparator • High-carbohydrate (low fat) diet for 6 weeks, 1 week washout followed by cross-over for 6 weeks All meals were prepared in the metabolic kitchens (2,000-kcal). The patients ate at least one meal per day at the metabolic units on weekdays; the remaining food was supplied in packages to be consumed at home. To monitor compliance, the patients were instructed to bring back any unconsumed food, were interviewed by dietitians, and were weighed during their visits. The patients were instructed to maintain their usual level of physical activity and salt intake. The energy intake was adjusted if needed to maintain constant body weight during the study.
Outcomes	Assessments (3): baseline and weeks 6 and 13 **Primary outcome measures** 1. Blood pressure ✱ 2. Heart rate **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 2611: "This study was supported in part by a grant from Pfizer (New York, NY); National Institutes of Health Grants M01-RR00633, MO1-RR-00400, M01-RR-00827, M01-RR00070, HL-29252, HL-08506, and DK-38949; and the Medical Research Service of the San Diego (CA) Veterans Affairs Medical Center"
Declaration of interest	None declared
Notes	Medication: the blood pressure medications of patients remained stable throughout the study. No information on antidiabetic medication. High cis-monounsaturated fat (low carbohydrate) diet: 40 en% carbohydrates, 15 en% protein, 45 en% fat High-carbohydrate (low fat) diet: 55 en% carbohydrates, 15 en% protein, 30 en% fat Data from both study periods are pooled and no separate data per study period are available. Wash-out period is to short. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Shah 2005 (88)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 2608): "A randomized, cross-over study was designed". Comment; Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. All meals were prepared in the metabolic kitchens (2,000-kcal). The patients ate at least one meal per day at the metabolic units on

		weekdays; the remaining food was supplied in packages to be consumed at home. To monitor compliance, the patients were instructed to bring back any unconsumed food, were interviewed by dietitians, and were weighed during their visits. The patients were instructed to maintain their usual level of physical activity and salt intake. The energy intake was adjusted if needed to maintain constant body weight during the study. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported, but of one there are no blood pressure data. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was a too short wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Shai 2008 (89)

Methods	Randomized controlled trial (DIRECT) Dietary Interventions Randomized Controlled Diet <u>Setting</u> Research center with an on-site medical clinic, Dimona, Israel <u>Date of study</u> July 2005 until June 2007. Study duration 2 years
Participants	N = 322 (277 men, 45 women) Mean age: 52 years **<u>Inclusion criteria of the trial</u>** 1. Age between 40 and 65 years 2. BMI ≥ 27 or the presence of type 2 diabetes according to the American Diabetes Association criteria or coronary heart disease, regardless of age and BMI **<u>Exclusion criteria of the trial</u>** 1. Pregnant or lactating 2. Serum creatinine level ≥ 2 mg/dl (177 μmol/liter) 3. Liver dysfunction (an increase by a factor of ≥ 2 above the upper limit of normal in alanine aminotransferase and aspartate aminotransferase levels) 4. Gastrointestinal problems that would prevent them from following any of the test diets 5. Active cancer

	6. Participating in another diet trial Withdrawals/losses to follow-up 50/322 (11.5%); 24/109 in low carbohydrate diet group, 10/104 in low fat diet group, 16/109 in Mediterranean diet group • Lack of motivation: 11 in low carbohydrate diet group, 7 in low fat diet group, 9 in Mediterranean diet group • Disappointed with assigned diet: 4 in low carbohydrate diet group, 0 in low fat diet group, 2 in Mediterranean diet group • Sabbatical: 1 in low carbohydrate diet group, 1 in low fat diet group, 0 in Mediterranean diet group • Personal reasons: 8 in low carbohydrate diet group, 2 in low fat diet group, 5 in Mediterranean diet group Baseline data (SD) of the whole group including those with diabetes Having diabetes: 46/322 (14.3%);19/109 in low carbohydrate diet group, 12/104 in low fat diet group, 15/109 in Mediterranean diet group Weight (kg): low carbohydrate diet group 91.8 (14.3), in low fat diet group 91.3 (12.3), in Mediterranean diet group 91.1 (13.6) BMI (kg/m²): low carbohydrate diet group 30.8 (3.5), in low fat diet group 30.6 (3.2), in Mediterranean diet group 31.2 (4.1) Systolic blood pressure (mm Hg): low carbohydrate diet group 130.8 (15.1), in low fat diet group 129.6 (13.2), in Mediterranean diet group 133.1 (14.1) Diastolic blood pressure (mm Hg): low carbohydrate diet group 79.4 (9.1), in low fat diet group 79.1 (9.1), in Mediterranean diet group 80.6 (9.2) Waist circumference (cm): low carbohydrate diet group 106.3 (9.1), in low fat diet group 105.3 (9.3), in Mediterranean diet group 106.2 (9.1) LDL cholesterol (mg/dl): low carbohydrate diet group 117.2 (34.5), in low fat diet group 117.0 (35.6), in Mediterranean diet group 122.8 (34.4) HDL cholesterol (mg/dl): low carbohydrate diet group 38.5 (9.2), in low fat diet group 38.6 (9.6), in Mediterranean diet group 39.4 (9.4) Triglycerides (mg/dl): low carbohydrate diet group 181.7 (116.9), in low fat diet group 156.5 (62.4), in Mediterranean diet group 173.6 (67.7) Fasting plasma glucose (mg/dl): low carbohydrate diet group 92.6 (28.5), in low fat diet group 86.9 (26.0), in Mediterranean diet group 94.3 (38.1)
Interventions	**Intervention** • Low carbohydrate diet for 2 years (n = 109) **Comparator 1** • Low fat diet for 2 years (n = 104) **Comparator 2** • Mediterranean diet for 2 years (n = 109) The low-carbohydrate, non–restricted-calorie diet aimed to provide 20 g of carbohydrates per day for the 2-month induction phase and immediately after religious holidays, with a gradual increase to a maximum of 120 g per day to maintain the weight loss. The intakes of total calories, protein, and fat were not limited. However, the participants were counselled to choose vegetarian sources of fat and protein and to avoid trans-fat. The diet was based on the Atkins diet The low-fat, restricted-calorie diet was based on American Heart Association guidelines aiming at an energy intake of 1500 kcal per day for women and 1800 kcal per day for men, with 30% of calories from fat, 10% of calories from saturated fat, and an intake of 300 mg of cholesterol per day. The participants were counselled to consume low-fat grains, vegetables, fruits, and legumes and to limit their consumption of additional fats, sweets, and high-fat snacks

	The moderate-fat, restricted-calorie, Mediterranean diet was rich in vegetables and low in red meat, with poultry and fish replacing beef and lamb. We restricted energy intake to 1500 kcal per day for women and 1800 kcal per day for men, with a goal of no more than 35% of calories from fat; the main sources of added fat were 30 to 45 g of olive oil and a handful of nuts (five to seven nuts, <20 g) per day. Each diet group was assigned a registered dietitian who led all six subgroups of that group. The dietitians met with their groups in weeks 1, 3, 5, and 7 and thereafter at 6-week intervals, for a total of 18 sessions of 90 minutes each. In order to maintain equal intensity of treatment, the workshop format and the quality of the materials were similar among the three diet groups, except for instructions and materials specific to each diet strategy. Six times during the 2-year intervention, another dietitian conducted 10-to-15-minute motivational telephone calls with participants who were having difficulty adhering to the diets Adherence to the diets was evaluated by a validated food-frequency questionnaire24 that included 127 food items and three portion-size pictures for 17 items
Outcomes	Assessments (3): baseline, month 3, 6, 12 and 24 (weight each months, blood pressure every 3 months) **Primary outcome measures** 1. Weight ✱ 2. BMI ✱ 3. Waist circumference ✱ 4. Cholesterol, LDL, HDL, triglycerides ✱ 5. Fasting plasma glucose/insulin ✱ 6. Plasma high-sensitivity C-reactive protein 7. Plasma high-molecular-weight adiponectin 8. Plasma leptin 9. Liver function tests 10. HOMA-IR 11. HbA1c in the diabetic patients (data for n = 36) ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote age 241: "Supported by the Nuclear Research Center Negev (NRCN), the Dr. Robert C. and Veronica Atkins Research Foundation, and the S. Daniel Abraham International Center for Health and Nutrition, Ben-Gurion University, Israel."
Declaration of interest	Quote page 241: "No potential conflict of interest relevant to this article was reported."
Notes	Medication: oral diabetic medications: low carbohydrate diet group 13 (12%), low fat diet group 6 (6%), in Mediterranean diet group 7 (6%) Insulin treatment: low carbohydrate diet group 2 (2%), low fat diet group 2 (2%), in Mediterranean diet group 0 (0%) Low-carbohydrate diet < 20 g and later 120 gram carbohydrates. Actual intake at 6 months: 41.4 en% carbohydrates, 21.6 en% protein, 38.8 en% fat (total adds up to 101.8 en%), at 12 months: 41.6 en% carbohydrates, 21.5 en% protein, 38.5 en% fat (total adds up to 101.6 en%), at 24 months: 40.4 en% carbohydrates, 21.8 en% protein, 39.1 en% fat (total adds up to 101.3 en%) Low fat diet < 30% fat: Actual intake at 6 months: 50.4 en% carbohydrates, 19.6 en% protein, 30.7 en% fat (total adds up to 100.7 en%), at 12 months 50.5 en% carbohydrates, 19.4 en% protein, 30.8 en% fat (total adds up to 100.7 en%), at 24

	months 50.7 en% carbohydrates, 19.0 en% protein, 30.0 en% fat (total adds up to 99.7 en%) Mediterranean diet: Actual intake 49.8 en% carbohydrates, 18.9 en% protein, 33.2 en% fat (total adds up to 101.9 en%), at 12 months 50.0 en% carbohydrates, 18.9 en% protein, 32.9 en% fat (total adds up to 101.8 en%), at 24 months 50.2 en% carbohydrates, 18.8 en% protein, 33.1 en% fat (total adds up to 102.1 en%) There are only separate data in diabetics for fasting glucose and HbA1c, therefore we cannot use the other outcomes as results cannot be extrapolated to type 2 diabetic population which accounted for only 14.3% of the total of included patients

Risk of bias table of Shai 2008 (89)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 230): "The participants were randomly assigned within strata of sex, age (below or above the median), BMI (below or above the median), history of coronary heart disease (yes or no), history of type 2 diabetes (yes or no), and current use of statins (none, <1 year, or ≥1 year) with the use of Monte Carlo simulations". Comment: Probably done.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. All groups received intensive sessions and regular follow-up with dietitians. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	50/322 (11.5%); 24/109 (22%) in low carbohydrate diet group, 10/104 (9.6%) in low fat diet group, 16/109 (14.5%) in Mediterranean diet group, number of drop-outs not completely balanced. Intention-to-treat analysis. Comment: We judged this as at an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at ClinicalTrials.gov number, NCT00160108, and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Simpson 1979 (90)

Methods	Randomized controlled, cross-over study Setting Departments of the Regius Professor of Medicine and Social and Community Medicine, University of Oxford, Radcliffe Infirmary, Oxford, UK Date of study Not specified. Study duration 6 weeks, no washout period, followed by cross-over for 6 weeks
Participants	N = 18 (15 men, 3 women) Mean age (SE): 54 (2.0) years **Inclusion criteria of the trial** 1. Established maturity-onset diabetes **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up 4/18; no adherence to study diet Baseline data (SD) Not specified
Interventions	**Intervention** • Low carbohydrate diet for 6 weeks, followed by crossover for 6 weeks **Comparator** • High carbohydrate (low fat) diet for 6 weeks, followed by crossover for 6 weeks Diets were iso-energetic
Outcomes	Assessments (3): baseline and weeks 6 and 12 **Primary outcome measures** 1. Fasting plasma glucose ✱ 2. Triglycerides ✱ 3. HbA1c ✱ 4. Cholesterol, HDL, LDL and VLDL ✱ 5. Weight ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 1756: "Financial support is provided by the British Diabetic Association, the Flora Information Service, ICI, and the International Sugar Research Foundation."
Declaration of interest	None declared
Notes	Medication: all were considered to be clinically and chemically stable (14 taking sulphonylureas and the remainder dietary treatment alone Low carbohydrate diet: 40 en% carbohydrates. Actual intake 34 en% carbohydrates, 16 en% protein, 50 en% fat High carbohydrate (low fat) diet: 60 en% carbohydrates. Actual intake 61 en% carbohydrates, 16 en% protein, 23 en% fat Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is more than 38 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Simpson 1979 (90)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1754): "analysed. They were then allocated at random to one of two groups." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	High risk	4/18 (22.2%), due to non-adherence Comment: We judged this as at high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Simpson 1981 (91)

Methods	Randomized controlled, cross-over study <u>Setting</u> Diabetes Research Laboratories and Department of Community Medicine and General Practice, University of Oxford, UK <u>Date of study</u> Unspecified. Study duration 6 weeks, no washout period, followed by cross-over for 6 weeks
Participants	N = 18 (10 men, 8 women). 9 insulin-dependent diabetics (IDDM) were studied separately, we only report on the NIDDM patients Mean age: 52.5 years

	Inclusion criteria of the trial 1. Non-insulin-dependent diabetes 2. Age between 20-70 years 3. Free from other major illness **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SD) Not specified
Interventions	**Intervention** • Low carbohydrate diet for 6 weeks, followed by crossover for 6 weeks **Comparator** • High carbohydrate (low fat) high in leguminous and cereal fiber diet for 6 weeks, followed by crossover for 6 weeks The diets were isocaloric with 1920 kcal per day. In the first two weeks after recruitment the aims of the study were discussed with each volunteer and instructions given about the diets and methods of preparation. It was necessary to give detailed advice about both diets for optimal adherence
Outcomes	Assessments (3): baseline and weeks 4 and 8 **Primary outcome measures-24 h metabolic profile** 1. Fasting plasma glucose/insulin ✱ 2. Triglycerides ✱ 3. HbA1c ✱ 4. Cholesterol, HDL, LDL and VLDL ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 5 : "We thank ..... the British Diabetic Association, the Simon Broome Heart Research Trust, and Mars for their financial support"
Declaration of interest	None declared
Notes	Medication: 14 patients were on sulphonylureas, 1 of these being on metformin also, and 4 were on diet alone Low carbohydrate diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat. Actual intake was 40-21-39% respectively. Daily fiber 14.2 g High carbohydrate (low fat) high in leguminous and cereal fiber diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat. Actual intake was 61-21-18% respectively. Daily fiber 105 g Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is more than 35 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table Simpson 1981 (91)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2): "randomised to start" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	In the first two weeks after recruitment the aims of the study were discussed with each volunteer and instructions given about the diets and methods of preparation. Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Simpson 1982 (92)

Methods	Randomized controlled, cross-over study Setting Diabetic Clinic, Oxford, UK Date of study Unspecified. Study duration 4 weeks, no washout, followed by cross-over for 4 weeks
Participants	N = 10 (8 men, 2 women) Mean age: 58 years (range 45-68) **Inclusion criteria of the trial** 1. Type 2 diabetes mellitus **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SD) Not specified
Interventions	**Intervention**

	• Low carbohydrate diet for 4 weeks, followed by crossover for 4 weeks **Comparator** • High carbohydrate (low fat) diet for 4 weeks, followed by crossover for 4 weeks
Outcomes	Assessments (3): baseline and weeks 4 and 8 **Primary outcome measures 24 h metabolic profiles** 1. Fasting plasma glucose ✱ 2. Triglycerides ✱ 3. HbA1c ✱ 4. Cholesterol, HDL, LDL and VLDL ✱ 5. Weight ✱ **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 238 : "the British Diabetic Association, the Simon Broome Heart Research Trust, the Flora Information Service, Mars Ltd. and The Sugar Association for their financial support"
Declaration of interest	None declared
Notes	Medication: eight were on sulphonylurea drugs (four on glibenclamide, three on chlorpropamide and one on tolbutamide) and two were treated by diet alone Low carbohydrate diet: 35 en% carbohydrates, 20 en% protein, 45 en% fat. Mean total dietary fiber intake of the ten patients was 14.3 g/24 h. High carbohydrate (low fat) diet: 60 en% carbohydrates, 20 en% protein, 20 en% fat. Mean fiber intake was still only 16.8 g/24 h. Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is more than 35 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias Table of Simpson 1982 (92)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote page 236: "They were randomised to start either the high or low carbohydrate diet." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may affect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.

Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Tay 2014 (93)

Methods	Randomized controlled study Setting Commonwealth Scientific and Industrial Research Organization (CSIRO) Clinical Research Unit in Adelaide, Australia Date of study May 2012 until February 2013. Study duration 24 weeks
Participants	N = 115 (66 men, 49 women) Mean age (SD): 58 (7) years **Inclusion criteria of the trial** 1. Overweight adults with type 2 diabetes mellitus 2. Age 35-68 years 3. BMI (kg/m²): 26-45 4. HbA1c ≥ 7.0% **Exclusion criteria of the trial** 1. Type 1 diabetes 2. Proteinuria (urinary albumin to creatinine ratio $30 mg/mmol) 3. Impaired renal function (eGFR ,60mL/min) 4. Abnormal liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or g-glutamyl transferase [GGT] ≥2.5 times the normal upper limit) assessed at screening 5. Any significant endocrinopathy (other than stable treated thyroid disease) 6. History of malignancy (other than nonmelanoma) 7. Liver, respiratory, gastrointestinal, or cardiovascular disease; pregnancy or lactation 8. Clinical depression; history of/or current eating disorder; or smoking Withdrawals/losses to follow-up 22/115 (19.1%); 12/58 in very low carbohydrate diet group, 10/57 in low fat diet group • Lost to follow-up: 5 in very low carbohydrate diet group, 3 in low fat diet group • Time constraints: 4 in very low carbohydrate diet group, 0 in low fat diet group • Work commitments: 2 in very low carbohydrate diet group, 2 in low fat diet group

	• Unable to comply with diet: 1 in very low carbohydrate diet group, 2 in low fat diet group • Health issue external to study: 0 in very low carbohydrate diet group, 2 in low fat diet group • Personal reasons: 0 in very low carbohydrate diet group, 1 in low fat diet group Baseline data (SD) Weight (kg): very low carbohydrate diet group 101.7 (14.4), high carbohydrate (low fat) diet group 101.6 (5.8) BMI (kg/m²): very low carbohydrate diet group 34.2 (4.5), high carbohydrate (low fat) diet group 35.1 (4.1) HbA1c (%): very low carbohydrate diet group 7.3 (1.1), high carbohydrate (low fat) diet group 7.4 (1.1) Waist circumference (cm): very low carbohydrate diet group 112.4 (10.6), high carbohydrate (low fat) diet group 112.5 (10.6) Fasting glucose (mmol/L): very low carbohydrate diet group 7.8 (2.1), high carbohydrate (low fat) diet group 8.4 (2.1) Systolic blood pressure (mmHg): very low carbohydrate diet group 130.4 (13.1), high carbohydrate (low fat) diet group 132.6 (13.2) Diastolic blood pressure (mmHg): very low carbohydrate diet group 80.0 (8.9), high carbohydrate (low fat) diet group 80.8 (10.1) Total cholesterol (mmol/L): very low carbohydrate diet group 4.5 (1.0), high carbohydrate (low fat) diet group 4.3 (1.0) LDL cholesterol (mmol/L): very low carbohydrate diet group 2.5 (0.9), high carbohydrate (low fat) diet group 2.4 (0.9) HDL cholesterol (mmol/L): very low carbohydrate diet group 1.2 (0.2), high carbohydrate (low fat) diet group 1.3 (0.3) Triglycerides (mmol/L): very low carbohydrate diet group 1.6 (0.7), high carbohydrate (low fat) diet group 1.4 (0.6)
Interventions	**Intervention** • Very low carbohydrate, high– unsaturated/low–saturated fat diet for 24 weeks (n = 58) **Comparator** • High–unrefined carbohydrate, low fat diet for 24 weeks (n = 57) Diet plans were individualized and matched for energy levels with moderate restriction (500–1,000 kcal/day). Diets were structured to include specific foods, listed in a quantitative food record that participants completed daily. To facilitate compliance, participants met individually with a dietitian biweekly for 12 weeks and monthly thereafter. Dietitians provided dietary advice and instruction on the eating plan and reporting requirements. Under supervision of exercise professionals, participants undertook, free of charge, 60-min structured exercise classes on 3 nonconsecutive days per week, incorporating moderate-intensity aerobic/resistance exercises, consistent with diabetes management guidelines. Attendance records were kept and participants were encouraged to make up any missed sessions. Apart from the planned exercise program, participants were instructed to maintain habitual physical activity levels.
Outcomes	Assessments (2): baseline and week 24 **Primary outcome measures** 1. HbA1c ✱ **Secondary outcome measures** 1. Glycemic variability 2. Antiglycemic medication changes

	3. Blood lipids (total cholesterol, LDL, HDL, triglycerides) ✱ 4. Blood pressure ✱ 5. Weight ✱ 6. Fasting blood glucose ✱ 7. Waist circumference ✱ ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 2917: "This study was supported by National Health and Medical Research Council project grant 103415. J.T. was supported by a postgraduate research scholarship from the Agency for Science, Technology and Research (A*STAR). No sponsor or funding source had a role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript."
Declaration of interest	Quote page 2917: "No potential conflicts of interest relevant to this article were reported".
Notes	Medications: 87 used metformin, 12 insulin, 36 sulphonylurea, 6 thiazolidinediones, equally balanced between groups, which were diminished/adjusted over the study period. Also lipid lowering medication and antihypertensive medication was used by over half of the study population. Very low carbohydrate, high– unsaturated/low–saturated fat diet: 14 en% carbohydrates, 28 en% protein, 58 en% fat. Actual intake 13.9 en% carbohydrates, 26.7 en% protein, 54.1 en% fat (total adds up to 94.7%) High–unrefined carbohydrate, low fat diet: 53% en% carbohydrates, 17 en% protein, <30 en% fat. Actual intake 50.1 en% carbohydrates, 18.8 en% protein, 24.5 en% fat (total adds up to 93.4%) Saturated fat was limited to <10% in both diets The four studies Tay 2015, Tay 2016, Brinkworth 2016, Wycherley 2016, Tay 2018 (copublications on same study population) provided data on additional outcomes

Risk of bias table of Tay 2014 (93)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 2910): "In a parallel design, participants were block matched for age, sex, BMI, HbA1c, and antiglycaemic medication using random varying block sizes before random computer-generated assignment to either an LC or HC diet in a 1:1 ratio". Comment: Probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 2910): "Randomization procedures (sequence generation and allocation concealment) were performed by research associates independent of outcome assessments and intervention delivery." Comment: There was insufficient information to permit a clear judgement. After e-mail communication: "The research associates who conducted the computer-generated randomization were separate from the research staff (e.g. Nurses, Dietitians) who were involved in the delivery of the intervention. Accessibility to this information was limited by password control, and a locked office."

		Comment: Allocation appears to have been adequately concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 2910): "Although diet assignment was discernible by participants and interventionists, blinding was maintained for outcome assessment and data analysis. Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Both received intensive advice and instruction of dietitians and received same amount of exercise (supervised). However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 2910): "Although diet assignment was discernible by participants and interventionists, blinding was maintained for outcome assessment and data analysis. Comment: The outcome measurements were not likely to be influenced.
Incomplete outcome data (attrition bias)	Unclear risk	22/115 (19.1%); 12/58 in very low carbohydrate diet group, 10/57 in low fat diet group. Per-protocol analysis Comment: The moderate drop-out rate combined with a per-protocol analysis poses an unclear risk of bias.
Selective reporting (reporting bias)	Unclear risk	The protocol of the study was available at www.anzctr.org.au (ACTRN12612000369820) and the prespecified outcomes and those mentioned in the methods section appeared to have been reported. However, data of their primary outcome HbA1c were not presented on the whole population, but were divided in those with a higher HbA1c and those with lower HbA1c. Recalculating these data for the whole group showed no difference between the two diets for this outcome. Comment: We judged this as at a unclear risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Walker 1995 (94)

Methods	Randomized controlled, cross-over study Setting School of Nutrition and Public Health, Deakin University, Geelong and Burwood, and the Department of Medicine, University of Melbourne, the Geelong Hospital, Geelong, Australia. Date of study Unspecified. Study duration 3 months, one month washout, followed by 3 months cross-over
Participants	N = 24 (9 men, 15 women) completed the study (unclear how many started) mean age (SE): 58.3 (2.1) years **Inclusion criteria of the trial** 1. Non-insulin dependent type 2 diabetes mellitus **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None declared

	Baseline data (SE) Weight (kg): modified fat (low carbohydrate) diet group 80.1 (2.9), high-carbohydrate low-fat diet group 79.5 (3.0) BMI (kg/m²): modified fat (low carbohydrate) diet group 29.1 (0.7), high-carbohydrate low-fat diet group 28.8 (0.7) Systolic blood pressure (mmHg): modified fat (low carbohydrate) diet group 133 (3), high-carbohydrate low-fat diet group 132 (3) Diastolic blood pressure (mmHg): modified fat (low carbohydrate) diet group 77 (2), high-carbohydrate low-fat diet group 75 (3) Fasting glucose (mmol/L): modified fat (low carbohydrate) diet group 9.6 (0.8), high-carbohydrate low-fat diet group 8.5 (0.6) Triglycerides (mmol/L): modified fat (low carbohydrate) diet group 2.36 (0.46), high-carbohydrate low-fat diet group 2.24 (0.29) HDL cholesterol (mmol/L): modified fat (low carbohydrate) diet group 0.99 (0.05), high-carbohydrate low-fat diet group 1.02 (0.05) LDL cholesterol (mmol/L): modified fat (low carbohydrate) diet group 3.81 (0.17), high-carbohydrate low-fat diet group 3.62 (0.18) HbA1c (%): modified fat (low carbohydrate) diet group 6.8 (0.4), high-carbohydrate low-fat diet group 6.4 (0.3)
Interventions	After 1 month on their usual diet patients were randomized **Intervention** • Modified fat (low carbohydrate) diet for 3 months, 1 month washout followed by cross-over for 3 months **Comparator** • High-carbohydrate low-fat diet for 3 months, 1 month washout followed by cross-over for 3 months Subjects completed 7-day weighed food records (1/month), which were analyzed by a dietitian using the System for On-line Dietary Analysis based on Australian food tables Reported energy intake remained similar on both diets
Outcomes	Assessments (5): baseline, day 4, months 3, 4, and 7 **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Body weight/BMI ✱ 3. Blood pressure ✱ 4. HbA1c ✱ 5. Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, VLDL cholesterol ✱ 6. Free fatty acids 7. Questionnaire on acceptance of the diets **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 403: "This study was supported by a grant from Diabetes Australia. We are grateful for products supplied by the International Olive Oil Council and Meadow Lea Foods Australia."
Declaration of interest	None declared
Notes	Medication: they controlled their diabetes by low-dose oral hypoglycemic agents or by diet alone.

	Modified fat (low carbohydrate) diet: 40 en% carbohydrates, 14 en% protein, 36 en% fat. (Prescription was 40%-20%-40%) High carbohydrate (low fat) diet: 50% en% carbohydrates, 17 en% protein, 23 en% fat. (Prescription was 59%-20%-21%)

Risk of bias table of Walker 1995 (94)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 401): "in a random crossover design". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups. After e-mail communication: "Sequence generation was generated by reference to a table of random numbers" Comment: Probably done.
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement. After e-mail communication: The table was in a locked drawer and a third person not involved in the study provided each time the next number to the investigator. Comment: Allocation appears to have been adequately concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	None declared, however, it is unclear how many initially were randomized, the report mentioned 24 participants completed the study. Comment: We judged this as at an unclear risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Ward 1982 (95)

Methods	Randomized controlled, cross-over study Setting

	Diabetes Research Laboratories, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford, U Date of study Not specified. Study duration 6 weeks, no washout period, followed by cross-over for 6 weeks
Participants	N = 7 (gender not reported) Mean age (SE): 55 (2.0) years **Inclusion criteria of the trial** 1. Non-insulin-dependent diabetes **Exclusion criteria of the trial** 1. Not specified Withdrawals/losses to follow-up None reported Baseline data (SD) Not specified
Interventions	Previously been stabilized on a standard low carbohydrate diet **Intervention** • Low carbohydrate diet for 6 weeks, followed by crossover for 6 weeks **Comparator** • High carbohydrate (low fat) diet for 6 weeks, followed by crossover for 6 weeks
Outcomes	Assessments (3): baseline and weeks 6 and 12 **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. Fasting blood for determination of monocyte insulin receptor binding **Secondary outcome measures** 1. Not specified ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 96: "This work was supported in part by Flora Information Service and by the Oxfordshire Regional Health Authority."
Declaration of interest	None declared
Notes	Medication: four were taking oral hypoglycemics, the doses unchanged throughout the study, and three were on diet alone. Low carbohydrate diet: 40 en% carbohydrates, 20 en% protein, 40 en% fat High carbohydrate (low fat) diet: 60 en% carbohydrates, 22 en% protein, 18 en% fat Data from both study periods are pooled and no separate data per study period are available. No wash-out period. Study is more than 38 years old. We cannot use the data (see Supplemental Table 4)

Risk of bias table of Ward 1982 (95)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 93): "in random order". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported.

		Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	High risk	There was no wash out period between intervention periods. The metabolic effects of nutrients can persist for a variable length of time (depending on the nature of the nutrients). Therefore, carry over effects can bias the analysis of data obtained in the second intervention periods if the wash out period is too short. Furthermore, no separate data for first period/phase were available. Comment: We judged this as at high risk of bias.

Wolever 2008 (96)

Methods	Randomized controlled study Setting Multicenter Canada Date of study Unspecified. Study duration 1 year
Participants	N = 162 (74 men, 88 women) Mean age: 60 years **Inclusion criteria of the trial** 1. Men or nonpregnant women with T2DM 2. Fasting plasma glucose 7.0 mmol/L or plasma glucose11.1 mmol/L 2 h after a 75-g oral-glucose-tolerance test (OGTT) on1 occasion within 2 months of randomization 3. 35-75 years old 4. HbA1c 130% of the upper limit of normal and a body mass index (BMI; in kg/m²) of 24 to 40 **Exclusion criteria of the trial** 1. Use of insulin or any hypoglycemic or antihyperglycemic medication 2. Stroke 3. Myocardial infarction or major surgery within 6 months of randomization 4. Serum triacylglycerol concentrations 10 mmol/L 5. Any major debilitating disorder 6. Any condition or drug likely to alter nutrient absorption 7. Use of oral steroids, substance or alcohol abuse

	8. Allergy or intolerance to 1 of the study key foods 9. Expectation of being on vacation and unable to take study foods for 8 wk in a row or a total of 12 wk <u>Withdrawals/losses to follow-up</u> 32/162 (19.8%); 10/54 in low carbohydrate high MUFA diet group, 11/56 in high carbohydrate (low GI) diet group, 11/52 in high carbohydrate (high GI) diet group • Failed treatment; 4 in low carbohydrate high MUFA diet group, 5 in high carbohydrate (low GI) diet group, 2 in high carbohydrate (high GI) diet group • Refused to participate; 4 in low carbohydrate high MUFA diet group, 6 in high carbohydrate (low GI) diet group, 8 in high carbohydrate (high GI) diet group • Adverse events; 2 in low carbohydrate high MUFA diet group, 0 in high carbohydrate (low GI) diet group, 2 in high carbohydrate (high GI) diet group <u>Baseline data (SE)</u> BMI (kg/m²): low carbohydrate high MUFA diet group 31.1 (1.2), high carbohydrate (low GI) diet group 31.6 (0.6), high carbohydrate (high GI) diet group 30.1 (0.6) Weight (kg): low carbohydrate high MUFA diet group 84.7 (2.6), high carbohydrate (low GI) diet group 81.1 (2.5), high carbohydrate (high GI) diet group 84.4 (2.5) Waist circumference (cm): low carbohydrate high MUFA diet group 98.6 (3.0), high carbohydrate (low GI) diet group 98.3 (2.3), high carbohydrate (high GI) diet group 99.1 (3.0) HbA1c (%): low carbohydrate high MUFA diet group 6.1 (0.9), high carbohydrate (low GI) diet group 6.2 (0.8), high carbohydrate (high GI) diet group 6.2 (1.0) Fasting glucose (mmol/L): low carbohydrate high MUFA diet group 7.5 (0.2), high carbohydrate (low GI) diet group 7.1 (0.1), high carbohydrate (high GI) diet group 7.6 (0.5) Total cholesterol (mmol/L): low carbohydrate high MUFA diet group 5.01 (0.13), high carbohydrate (low GI) diet group 5.09 (0.13), high carbohydrate (high GI) diet group 4.86 (0.16) LDL-cholesterol (mmol/L): low carbohydrate high MUFA diet group 3.02 (0.10), high carbohydrate (low GI) diet group 3.02 (0.13), high carbohydrate (high GI) diet group 2.82 (0.13) HDL-cholesterol (mmol/L): low carbohydrate high MUFA diet group 1.16 (0.05), high carbohydrate (low GI) diet group 1.21 (0.03), high carbohydrate (high GI) diet group 1.14 (0.5) Triglycerides (mmol/L): low carbohydrate high MUFA diet group 1.79 (0.11), high carbohydrate (low GI) diet group 1.87 (0.10), high carbohydrate (high GI) diet group 2.07 (0.15) Systolic blood pressure (mmHg): low carbohydrate high MUFA diet group 127 (3), high carbohydrate (low GI) diet group 124 (4), high carbohydrate (high GI) diet group 129 (2) Diastolic blood pressure (mmHg): low carbohydrate high MUFA diet group 78 (2), high carbohydrate (low GI) diet group 77 (2), high carbohydrate (high GI) diet group 78 (1)
Interventions	**<u>Intervention</u>** • Low carbohydrate high-monounsaturated fat diet for 1 year (n = 54) **<u>Comparator 1</u>** • High carbohydrate low glycemic index (low fat) diet for 1 year (n = 56) **<u>Comparator 2</u>** • High carbohydrate high glycemic index (low fat) diet for 1 year (n = 52) Subjects in each diet group could choose from 16–21 key foods, which were provided free of charge. Intake was recorded daily in key-food diaries. Subjects received individualized advice from a registered dietitian at each visit. General advice on following a heart-healthy diet was provided to all subjects. Each subject had an

	individualized education session with the dietitian about the dietary intervention he or she was to follow on the day of the first metabolic profile (the day of randomization). This session lasted for 30–60 min, during which time the previously collected food records were reviewed and the study protocol explained. All subjects were given a list of the key foods for their respective study diet, and the list indicated the number of servings they were to consume each day. Subjects were seen 2 and 4 wk after randomization and then every 4 wk for weighing, review of key-food diaries, and pick-up of supplies of key foods. During each 30-min visit, dietitians provided individualized dietary advice and discussed any challenges that subjects encountered in following the study protocol and their solutions. Three-day food records were recorded twice during the run-in period and at 1, 3, 6, 9, and 12 months after randomization.
Outcomes	Assessments (15): baseline and weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 **Primary outcome measures** 1. Fasting plasma glucose/fasting plasma insulin ✱ 2. HbA1c ✱ 3. Serum cholesterol, triacylglycerol, apolipoprotein (apo) A-I, and apo B, HDL cholesterol, LDL cholesterol ✱ 4. CRP **Secondary outcome measures** 1. Weight ✱ 2. Waist circumference ✱ 3. Systolic and diastolic blood pressure ✱ ✱ Denotes outcomes prespecified for this review
Funding source	Quote page 114: "Supported by the Canadian Institutes of Health Research (CIHR-MCT- 44205). Key foods were donated by Kellogg Canada Inc, Robin Hood (division of Smucker Foods of Canada Co), HJ Heinz Co, Italpasta Ltd, Uncle Ben's Rice (division of Mars Inc), Kraft Foods Inc, Dainty Foods Inc (division of MRRM Inc), the Almond Board of California, and the National Peanut Board.
Declaration of interest	Page 124: "TMSW, ALG, J-LC, RGJ, LAL, PM, NWR, and EAR: obtained funding; and TMSW, ALG, CM, and PWC: administrative, technical, or material support. TMSW is president and part owner of Glycemic Index Laboratories Inc, a contract research organization, and president and part-owner of Glycaemic Index Testing Inc, a corporation that provides services related to the measurement of the glycemic index of foods. He has received grant or research support from Cargill Inc and ILSI Europe; was a consultant for the US Potato Board; and received honoraria for consulting or speaking from the Dutch Sugar Bureau and Mars Inc. TMSW is co-author of a range of popular books on the glycemic index under the general title of The Glucose Revolution: Authoritative Guide to the Glycemic Index, published by Marlowe & Co (New York, NY) and the author of a scientific book entitled The Glycaemic Index: A Physiologic Classification of Dietary Carbohydrate, published by CABI (London, United Kingdom). None of the other authors had any personal or financial conflict of interest."
Notes	No use of medication for the diabetes Low carbohydrate high-monounsaturated fat diet: 39.3 en% carbohydrates, 20.6 en% protein, 40.1 en% fat (actual intake) High carbohydrate low glycemic index (low fat) diet: 51.9 en% carbohydrates, 21.6 en% protein, 26.5 en% fat (actual intake) High carbohydrate high glycemic index (low fat) diet: 46.5 en% carbohydrates, 22.7 en% protein, 30.8 en% fat (actual intake) Only the first two diets match our inclusion criteria for 'low carb' and 'low fat' diet respectively

	The study Wolever 2017 (copublications on same study population) provided data on quality of life

Risk of bias table of Wolever 2008 (96)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 115): "Subjects, stratified by center, were randomly assigned to 1 of the 3 diets with the use of blocks of various sizes to enhance allocation concealment...Randomization (generated by computer with the random seed chosen from a table of random numbers)..". Comment: Probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 115): "Treatment assignments were sealed in sequentially numbered opaque envelopes kept by a person not involved with the study". Comment: Allocation appears to have been adequately concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. Subjects in each diet group could choose from 16–21 key foods, which were provided free of charge. Subjects received individualized advice from a registered dietitian at each visit. General advice on following a heart-healthy diet was provided to all subjects. Follow-up meetings were similar for all groups. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.
Blinding of outcome assessment (detection bias)	Low risk	Nothing reported regarding blinding. However, outcome measurements were objective and unlikely to be influenced. Comment: The outcome measurements were not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	32/162 (19.8%) balanced between groups. But 156 were included in the analyses, 6 refused at follow up. Comment: We judged this as at an unclear risk of bias.
Selective reporting (reporting bias)	Unclear risk	The trial was registered on the Current Controlled Trials register (ISRCTN Reg. no. ISRCTN81151522 and the prespecified outcomes and those mentioned in the methods section appeared to have been reported except quality of life, which was one of our predefined outcomes. Comment: We judged this as at an unclear risk of bias.
Other bias	Low risk	There are no baseline imbalances between the two groups we are interested in (low carb and de high carbohydrate, low glycemic index diet group. The LDL cholesterol was slightly lower in the 3rd group. Comment: We judged this as an a low risk of bias.

Yamada 2014 (97)

Methods	Randomized controlled study Setting Diabetes Center, Kitasato Institute Hospital, Japan Date of study April 2011 until January 2012. Study duration 6 months
Participants	N = 24 (12 men, 12 women) Mean age: 63 years **Inclusion criteria of the trial** 1. Type 2 diabetes who were being treated in the outpatient clinic who had received guidance regarding calorie restriction at least once and whose HbA1c level at enrolment was 6.9-8.4%, suggesting that their blood glucose level was not adequately controlled **Exclusion criteria of the trial** 1. Proteinuria of >1.0 g/day 2. Serum creatinine level of >132 μmol/L (men) or 106 μmol/L (women) 3. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level of >3 times the upper limit of normal 4. History of myocardial infarction or stroke within six months before study entry 5. An absolute change in the HbA1c of >1.0% within six months before study entry Withdrawals/losses to follow-up None reported Baseline data (SD) HbA1c(%): low carbohydrate diet group 7.6 (0.4), calorie restricted (low fat) diet group 7.7 (0.6) Fasting plasma glucose (mg/dl): low carbohydrate diet group 138 (44), calorie restricted (low fat) diet group 155 (46) Weight (kg): low carbohydrate diet group 67 (15.9), calorie restricted (low fat) diet group 68.1 (7.7) BMI (kg/m²): low carbohydrate diet group 24.5 (4.3), calorie restricted (low fat) diet group 27.0 (3.0) LDL-cholesterol (mg/dl): low carbohydrate diet group 99.8 (28.2), calorie restricted (low fat) diet group 112.2 (20.5) Triglycerides (mg/dl): low carbohydrate diet group 141.7 (76.2), calorie restricted (low fat) diet group 155.2 (86.4) HDL-cholesterol (mg/dl): low carbohydrate diet group 62.8 (17.2), calorie restricted (low fat) diet group 59.8 (19.1) Systolic blood pressure (mm Hg): low carbohydrate diet group 124.4 (10.8), calorie restricted (low fat) diet group 124.9 (10.7) Diastolic blood pressure (mm Hg): low carbohydrate diet group 72.6 (6.2), calorie restricted (low fat) diet group 74.8 (10.1)
Interventions	**Intervention** • Low carbohydrate diet for 6 months (n = 12) **Comparator** • Calorie restricted (low fat) diet for 6 months (n = 12) To avoid any possible influence of the experience and consulting skills of the dieticians in this study, four registered dieticians instructed the patients in both groups. Low-carbohydrate diet: the total carbohydrate intake to be <130 g/day. To prevent ketosis the lower limit of carbohydrate intake was set to 70 g/day. To prevent postprandial hyperglycemia, the target carbohydrate content in each meal was 20-40 g, and the subjects were allowed to consume sweets containing 5 g of carbohydrates twice daily, thus resulting in a total carbohydrate intake of 70-130 g/day

	Calorie-restricted diet: patients received face-to-face guidance on how to calculate their calorie intake by classifying macronutrients. The target calorie intake was defined based on the Japan Diabetes Society recommendations
Outcomes	Assessments (4): baseline and weeks months 2, 4 and 6 **Primary outcome measures** 1. HbA1c ✱ 2. Fasting plasma glucose ✱ 3. Bodyweight ✱ 4. Incidence of hypoglycemic episodes **Secondary outcome measures** 1. Serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides ✱ 2. Blood pressure ✱ 3. Markers for atherosclerosis 4. Renal function 5. Liver enzymes 6. Quality of life, the patients completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Problem Areas In Diabetes (PAID) scale ✱ 7. Adverse events reported by the patients or noted by the investigators
Funding source	None declared
Declaration of interest	Quote page 18: "The authors state that they have no Conflict of Interest (COI)."
Notes	Medication: during the study period, medications were not changed, unless hypoglycemia occurred Low-carbohydrate diet: a total carbohydrate intake of 70-130 g/day. Actual intake 29.8 en% carbohydrates, 25.3 en% protein, 45.4 en% fat Calorie restricted diet: 50-60 en% carbohydrates, < 20 en% protein, < 25 en% fat. Actual intake 51.0 en% carbohydrates, 16.6 en% protein, 32.3 en% fat

Risk of bias table of Yamada 2014 (97)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 14): "The enrolled patients were randomly allocated to receive either a non-calorie-restricted, low-carbohydrate diet (hereafter low-carbohydrate diet) or calorie-restricted diet using a permuted randomised block of four patients per block". Comment: Probably done.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported. Comment: There was insufficient information to permit a clear judgement.
Blinding of participants and personnel (performance bias)	Unclear risk	Although both physicians and patients were aware which diet the patients were following, the patients appear to receive for the rest the same care of their physicians. However, we cannot rule out the effect of expectations of physicians and patients and how this may effect e.g. adherence to the diet. Comment: We judged this as at an unclear risk of bias.

Online Supporting Material (OSM) – Supplemental Table 6

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 14): "The patients and investigators were not masked to group assignment". However, majority of outcome measurements were objective and unlikely to be influenced, but the questionnaires were subjective and therefore likely to be influenced. Comment: We consider the risk of bias for this outcome to be unclear.
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	There was no baseline imbalance between groups for any of the parameters.

Supplemental Table 7 Systematic reviews
Systematic reviews and evidence syntheses focussing on the effects of low carbohydrate diets on metabolic outcome parameters

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