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

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ABSTRACT

Background: It remains uncertain which diet is best for people with type 2 diabetes (T2D).

Objective: We compared the effects of dietary carbohydrate restriction with fat restriction on markers of metabolic syndrome and quality of life in people with T2D.

Design: This systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCTs) compares the effects of a low-carbohydrate [≤40% of energy (%)] diet with those of a low-fat (≤30%) diet over a period of ≥4 wk in patients with T2D. Two investigators independently selected studies, extracted data, and assessed risk of bias. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was used to assess the certainty of evidence. Pooled mean differences (MDs) and 95% CIs were calculated with the use of a random-effects model.

Results: Thirty-three RCTs and 3 CCTs ($n = 2161$) were included. Glycated hemoglobin declined more in people who consumed low-carbohydrate food than in those who consumed low-fat food in the short term (MD: –1.38%; 95% CI: –2.64%, –0.11%; very-low-certainty evidence). At 1 y, the MD was reduced to –0.36% (95% CI: –0.58%, –0.14%; low-certainty evidence); at 2 y, 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 prespecified time points. There was little to no difference in LDL concentration or any of the secondary outcomes (body weight, waist circumference, blood pressure, quality of life) in response to either of the diets (very-low- to high-certainty evidence).

Conclusions: Currently available data provide low- to moderate-certainty evidence that dietary carbohydrate restriction to a maximum of 40% yields slightly better metabolic control of uncertain clinical importance than reduction in fat to a maximum of 30% in people with T2D. This systematic review is registered at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017052467 as CRD42017052467. *Am J Clin Nutr* 2018;108:1–32.

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

INTRODUCTION

Type 2 diabetes (T2D) 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 T2D, it remains unclear which dietary measures are most effective in ameliorating metabolic derangements. There is little doubt, however, that reduction in body fat stores dampens chronic inflammation and improves metabolic anomalies. Thus, it is perhaps unsurprising to note that dietary guidelines for T2D 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 2 assumptions. First, that because fat contains more calories per gram, consuming less fat will reduce fat stores more than restricting protein or carbohydrate intake, and second, that consumption of (saturated) fat is associated with dyslipidemia (elevated LDL-cholesterol concentrations) and

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Supplemental Tables 1–7 and Supplemental Figures 1–8 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CCT, controlled clinical trial; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HbA1c, glycated hemoglobin; MCS, mental component score; MD, mean difference; PAID, Problem Areas in Diabetes; PCS, physical component score; RCT, randomized controlled trial; T2D, type 2 diabetes; %, percentage of energy.

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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 T2D (4–6). This position concurs with common sense, because 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, because any excess glucose is readily converted into (saturated) fat by hepatic de novo lipogenesis and subsequently secreted as VLDL triglycerides (7), the restriction of starchy food is expected to reduce plasma triglyceride concentrations. 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, body weight, and plasma lipid profiles in people with T2D. Indeed, the majority of these compared the effects of carbohydrate-restricted with -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 with low-fat dietary interventions on glucose control and other important metabolic and anthropometric variables, as well as on quality of life in individuals with T2D. 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 with a low-fat diet over a period of ≥4 wk in adult patients (aged ≥18 y) with T2D. A low-carbohydrate diet was defined as any dietary intervention containing ≤40% of energy (%) from carbohydrate and a low-fat diet as one containing ≤30% from fat. The value of 40% from 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 cutoffs of energy percentages were eligible for inclusion. However, if the actual intake of any one of the macronutrients exceeded 2% above these limits, these data were not included in the final analysis. We also only included data from crossover trials that had incorporated wash-out periods of ≥4 wk 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., before the crossover), because we considered the risk of carryover effects to be prohibitive. We excluded studies that included people with other chronic diseases, except for hypertension or cardiovascular disease. Studies were also excluded if they included participants who were using systemic corticosteroids, had any (progressive) disease requiring hospital care, or included those with an eating disorder or any other disease necessitating special dietary requirements (except for 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 trial registers (www.isrctn.com/, www.clinicaltrials.gov, http://www.anzctr.org.au/, http://apps.who.int/trialsearch/, www.clinicaltrialsregister.eu). Two review authors (EJvZ 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 that had covered this clinical topic.

Study selection

Two of the authors (EJvZ 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 **Figure 1**.

Data extraction and risk-of-bias assessment

Two of the authors (EJvZ 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, sex, age, inclusion and exclusion criteria, number of dropouts and reasons for loss to follow-up, baseline data, medication for diabetes). Key details were extracted on the diet (% from carbohydrates, protein, and fat; program support measures and degree of compliance; targeted intake and actual intake; whether diets were isocaloric

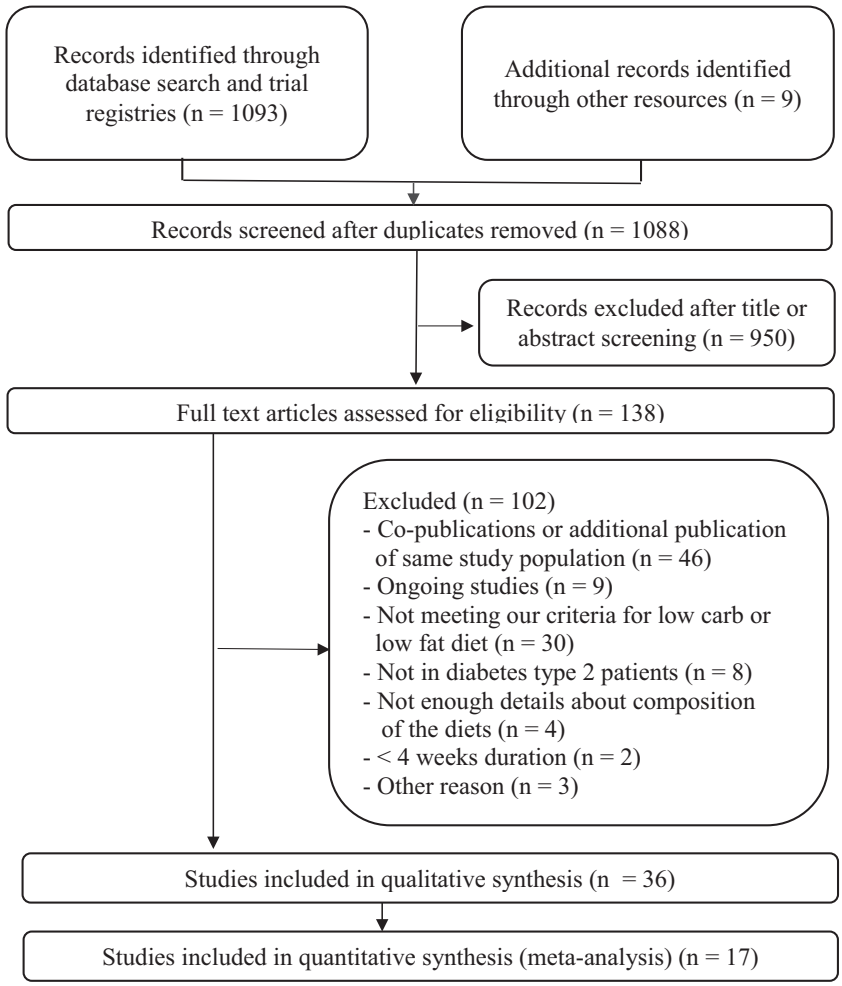

FIGURE 1 Study flow diagram. carb, carbohydrate.

and 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 <10 y old were contacted for additional trial details and missing data.

Our primary outcomes were change from baseline in glycated hemoglobin (HbA1c) concentration in whole blood and plasma glucose, triglyceride, and HDL- and LDL-cholesterol concentrations in the fasted condition. Our secondary outcomes were change from baseline in body weight, BMI, waist circumference, blood pressure, and quality of life. We grouped data in short-term (<8 wk), medium-low-term (≥8–16 wk), medium-high-term (≥16–26 wk), and long-term (>26 wk) measurements.

Two of the authors (EJvZ and ZF) independently assessed the risk of bias for each RCT with the use of the Cochrane Collaboration's domain-based assessment tool (11). Inconsistencies in judgments 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 ≥1 domain was classified as an unclear risk (plausible bias that raises some doubt about the results); and "high risk of bias" when ≥1 domain was judged as being at high risk (plausible bias that seriously weakens confidence in the results). For nonrandomized controlled trials we used ROBINS-I (7-domain tool) to assess the risk of bias (13). An overall risk of bias was assigned on the basis of 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 (MDs) with their associated 95% CIs, and carried out a complete case analysis if data were missing or incomplete. Heterogeneity between the studies in effect measures was assessed by using the I^2 statistic, with an $I^2 > 50\%$ indicative of substantial heterogeneity. We combined studies that evaluated similar outcomes and pooled their data in a meta-analysis independently of the observed heterogeneity. Following the recommendations of the GRADE working group, we considered downgrading the certainty of evidence for inconsistency when $I^2 > 50\%$, while taking other considerations for downgrading into

account (8). We intended to assess publication bias on the basis of 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, with the use of a random-effects model and presented in forest plots. All of the analyses were undertaken using RevMan 5.3 (The Nordic Cochrane Centre).

To explore sources of statistical heterogeneity between studies and to assess the robustness of our data, we conducted several sensitivity analyses. We repeated our analyses with the use of 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 with the use of GRADEpro GDT (http://gradepro.org) to assess the certainty of evidence for the predefined outcomes, as presented in the Summary of Findings (Tables 3–6). This approach takes into consideration the following: study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. Two of the authors (EJvZ 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 9 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 9 ongoing studies that had not published any data and 46 studies that were co-publications (studies that were 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 prespecified cutoffs) 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 T2D, that there were insufficient details reported on the content of the diets, or that the study duration was too short. For more details, see **Supplemental Tables 2–5**.

Study characteristics

Thirty-six studies (33 RCTs and 3 CCTs), which 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 judgments per risk-of-bias domain for each study. Four studies included only men, 3 included only women, and the remainder included both men and women in varying proportions. Samples sizes were rather small (ranging from <20 to 60 patients) in most of the studies, with only 8 studies evaluating >100 patients (66–68, 76, 86, 89, 93, 96). The mean age of participants was 56.6 y and was consistent across the studies (mean range: 32–65 y; majority between 50 and 60 y). A majority of the studies had a 2-arm design ($n = 31$), and the remainder included 3-arm studies ($n = 4$) and one 4-arm study. Most of the studies were conducted in Europe ($n = 14$) or in the United States and Canada ($n = 15$). One study was conducted in Mexico, 2 in Israel, 2 in Japan, and a further 2 in Australia. Study duration varied from 4 wk extending to 7 y in 1 outlying study, with an overall mean period of 33 wk (exclusion of the outlier would provide a more representative mean of 24 wk). A total of 19 studies were conducted before 2000, and the remaining 17 after the year 2000.

In 9 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 by Bozzetto et al. (63), which examined the effects of diet-exercise interaction, included a mandatory supervised exercise program in 2 of the 4 arms, but we only included data from the arms without exercise because 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 2 studies (89, 97) only one of the diets was calorie restricted. In 8 studies, the calorie intake was adjusted to maintain constant body weight (62–65, 70, 84, 88, 95).

The review included 17 crossover trials, and in 14 there was no washout, or the washout period was <4 wk, which we considered too short to exclude potential carryover effects. Because 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 carryover effects can bias the analysis of data obtained in the second intervention periods if the wash-out period is too short. The 3 remaining crossover studies had a

TABLE 1
Summary of characteristics of included studies and risk of bias[1]

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Blades, 1995 (62) (not included in results; see Supplemental Table 4)	RCT, cross-over (Dallas, TX)	10 men; mean age: 61.3 y; T2D; BMI (kg/m^2): 28.6	6 wk (crossover) A: High-MUFA (low-carbohydrate) diet; B: High-carbohydrate diet (low-fat) diet; 9-d washout in between; food prepared in metabolic kitchen, taken home; energy intake adjusted to keep constant body weight A: High-MUFA diet: 40% carbohydrates, 15% protein, 45% fat; B: High-carbohydrate (low-fat) diet: 55% carbohydrates, 15% protein, 30% fat No change in physical activity Medication: all patients were taking 17.8 ± 13 mg glipizide/d	Oral-fat-tolerance test; triacylglycerol and retinyl palmitate concentration; postheparin 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 y; T2D; BMI: 28–31	8 wk (we used arms A and B) A: High-MUFA (low-carbohydrate) diet (MUFA group) for 8 wk ($n = 8$); B: High-carbohydrate, high-fiber, low-glycemic-index (low-fat) diet (CHO/fiber group) for 8 wk ($n = 9$); C: High-MUFA (low-carbohydrate) diet plus physical training (MUFA + Ex group) for 8 wk ($n = 9$); D: High-carbohydrate, high-fiber, low-glycemic-index (low fat) diet plus physical training (CHO/fiber + Ex group) for 8 wk ($n = 10$) Frequent follow-up and support by dietitian; isoenergetic diets to keep body weight constant A: High-MUFA (low-carbohydrate) diet: 40% carbohydrates, 18% protein, 42% fat (fiber: 10 g/1000 kcal); B: High-carbohydrate (low-fat) diet: 52% carbohydrates, 18% protein, 30% fat (fiber: 28 g/1000 kcal); 26 of 45 used metformin in addition to diet	Liver fat content (^{1}H NMR) spectroscopy examination); HbA1c; fasting plasma glucose; fasting plasma triglycerides; fasting plasma cholesterol; fasting lipoprotein fractions; anthropometrics (body weight, height, and waist circumference); cardiorespiratory fitness; adherence to the dietary treatments	High risk (attrition 20%)
Chen, 1995 (64) (not included in results; see Supplemental Table 4)	RCT, crossover (Palo Alto, CA)	9 (6 men/3 women); mean age: 49 y; T2D; BMI: 27.5	6 wk (crossover) 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-wk dietary periods. Diets were isocaloric Low-carbohydrate diet: 40% carbohydrates, 15% protein, 45% fat; low-fat diet: 55% carbohydrates, 15% protein, 30% fat No medication (other than a sulfonylurea compound)	Fasting plasma glucose/fasting plasma insulin; fasting plasma triglycerides; retinyl ester concentrations; VLDL-triglyceride turnover; lipoprotein lipase measurement	High risk (no washout)
Coulston, 1989 (65) (not included in results; see Supplemental Table 4)	RCT, crossover (Palo Alto, CA)	8 (5 men/3 women); mean age: 66 y; T2D; BMI: 25.5	6 wk (crossover) 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-wk dietary periods Low-carbohydrate diet: 40% carbohydrates, 20% protein, 40% fat Low-fat diet: 60% carbohydrates, 20% protein, 20% fat No medication (other than a sulfonylurea 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)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Davis, 2009 (66)	RCT (Bronx, NY)	105 (23 men/82 women); mean age: 55 y; T2D; BMI: 35–37	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/wk A: Low-carbohydrate diet: 24% carbohydrates, 27% protein, 49% fat; B: Low-fat diet: 53% carbohydrates, 22% protein, 25% fat Recommendations to achieve 150 min of physical activity/wk Medication: at randomization, the algorithm included reducing insulin dosages by 50% and discontinuing sulfonylurea in the low-carbohydrate arm and reducing insulin by 25% and decreasing the sulfonylurea dose by 50% in the low-fat arm	Weight; glycemic control (HbA1c); blood pressure; fasting total cholesterol, HDL, LDL, triglycerides	Unclear risk (performance bias)
de Bont, 1981 (67)	RCT, multicenter (UK)	148 women; mean age: 55 y; T2D; weight: 72–73 kg	6 mo 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%; B: Low-fat diet: fat <30% Medication: oral hypoglycemic drugs: low- carbohydrate 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 sex unknown); mean age: 55 y; T2D; BMI: 31–31.8	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% carbohydrates, 20% protein, 45% fat; B: Low-fat diet (ADA): 50% carbohydrates, 20% protein, 30% fat; C: Traditional Mediterranean diet: 50% carbohydrates, 20% protein, 30% fat; 30–45 min of aerobic activity ≥3 d/wk Medication: no details of medication during the study but no insulin	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)
Garg, 1988 (69) (not included in results; see Supplemental Table 4)	RCT, crossover (Dallas, TX)	10 men; mean age: 56 y; T2D; BMI: 29	4 wk (crossover) A: High-MUFA (low-carbohydrate) diet; B: High-carbohydrate diet (low-fat) diet; 1–3 wk washout in between diets Patients hospitalized; food prepared in metabolic kitchen Diets were isocaloric A: High-MUFA diet: 35% carbohydrates, 15% protein, 50% fat; B: High-carbohydrate (low-fat) diet: 60% carbohydrates, 15% protein, 25% 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)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Garg, 1992 (70) (not included in results; Supplemental Table 4)	CCT, crossover (Dallas, TX)	10 men; mean age: 61.5 y; T2D; BMI: 27.7	4 wk (crossover) A: High-MUFA (low-carbohydrate) 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 body weight A: High-MUFA diet (liquid formula): 38% carbohydrates, 17% protein, 45% fat; B: High-carbohydrate (low-fat) diet (liquid formula): 65% carbohydrates, 15% protein, 20% fat Constant level of physical activity restricted to walking Medication: oral hypoglycemic drugs, if any, were discontinued	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)
Garg, 1994 (71) (not included in results; see Supplemental Table 4)	RCT, crossover, multicenter (USA)	42 (33 men/9 women); mean age: 58 y; T2D; BMI: 28.1	6 wk (crossover) A: High-MUFA (low-carbohydrate) diet; B: High-carbohydrate (low-fat) diet; 1-wk washout in between diets Food prepared at all centers Diets were isocaloric A: High-MUFA diet: 40% carbohydrates, 15% protein, 45% fat; B: High-carbohydrate (low-fat) diet: 55% carbohydrates, 15% protein, 30% fat Constant level of physical activity Medication: all patients were taking ±17 mg glipizide/d	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 y; T2D; BMI: 33.3	4 mo A: Very-low-calorie ketogenic diet ($n = 45$); B: Low-calorie (low-fat) diet ($n = 44$) Frequent follow-up and support by dietitian Calorie restricted A: Very-low-calorie ketogenic diet: carbohydrates <50 g; B: Low-calorie (low-fat) diet: 45–60% carbohydrates, 10–20% protein, <30% fat Recommendations to exercise and behavioral modifications Medication: oral antidiabetic medication was continued or diminished/stopped	Fasting plasma glucose; HbA1c, HOMA-IR; fasting plasma triglycerides, total cholesterol, LDL cholesterol; renal function, liver function, plasma uric acid, sodium, and potassium; body weight, BMI, waist circumference; dietary adherence and satisfaction	Unclear risk (selection bias, performance bias, attrition bias)
Guldbrand, 2012 (73)	RCT, multicenter (Sweden)	61 (27 men/34 women); mean age: 61 y; T2D; BMI: 31.6–33.8	2 y 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% carbohydrates, 30% protein, 50% fat Low-fat diet: 55–60% carbohydrates, 10–15% protein, 30% 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)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Gumbiner, 1998 (74)	CCT (Rochester, NY)	17 (8 men/9 women); mean age: 53 y; obese; T2D; BMI: 36.3–37.2	6 wk A: High-MUFA (low-carbohydrate) diet as liquid formula ($n = 8$); B: High-carbohydrate (low-fat) diet as a liquid formula ($n = 9$) Frequent follow-up and support in the Clinical Research Center Calorie restricted A: High-MUFA diet: 10% carbohydrates, 20% protein, 70% fat; B: High-carbohydrate (low-fat) diet: 70% carbohydrates, 20% protein, 10% fat Constant level of physical activity Medication: oral sulfonylurea agents, insulin, antihypertensive, and lipid-lowering therapies, were discontinued 2 wk before metabolic testing; insulin continued	Fasting plasma glucose; C-peptide, glucagon; total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoproteins A and B; weight	Moderate risk (confounding and performance bias)
Hockaday, 1978 (75)	RCT (Oxford, UK)	93 (52 men/41 women); mean age: 51.5 y; weight: 76.4–82.2 kg	1 y 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% carbohydrates, 20% protein, 40% fat Modified-fat, high-carbohydrate diet: 54% carbohydrates, 20% protein, 26% 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 (USA)	144 (129 men/15 women); mean age: 60 y; T2D; BMI: 36.9–38.1	2 y A: Low-carbohydrate diet ($n = 70$); B: Low-fat diet ($n = 74$) Regular follow-up and support by dietitian Low-carbohydrate diet: 30 g/d and deficit of 500 kcal/d Low-fat diet: <30% fat Regular exercise, 30 min, 5 d/wk recommended Medication: in low-carbohydrate group: sulfonylurea (57%), metformin (61.4%), thiazolidinediones (8.6%); in low-fat group: sulfonylurea (43.2%), metformin (52.7%), thiazolidinediones (10.8%)	Weight; plasma glucose and HbA1c; fasting plasma cholesterol; fasting triglycerides, LDL, HDL; blood pressure	High risk (attrition bias 52.3%)
Jones, 1986 (77) (not included in results; see Supplemental Table 4)	RCT, crossover (Oxford, UK)	10 (4 men/6 women); mean age: 64.5 y; T2D: blood glucose >12 mmol/L	6 wk (crossover) A: Low-carbohydrate diet; B: High-carbohydrate (low-fat), high-fiber diet No washout between diets A: Low-carbohydrate diet: 35% carbohydrates, 17% protein, 48% fat; B: High-carbohydrate (low-fat), high-fiber diet: 55% carbohydrates, 27% protein, 18% fat Medication: 7, chlorpropamide + metformin; 3, only chlorpropamide	Fasting plasma glucose, insulin; HbA1c; total cholesterol, cholesterol in the lipoprotein fractions; triglycerides; platelet phospholipid fatty acid measurements	High risk (no washout)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Lerman-Garber, 1995 (78)	RCT, crossover (Mexico City, Mexico)	20 women; mean age: 60 y; T2D; HbA1c >9.5%; poor glycemic control; BMI: 25.2	6 wk (crossover) A: High-MUFA (low-carbohydrate) diet; B: High complex carbohydrate (low-fat) diet 6-wk washout in between diets Regular follow-up and support by dietitian A: High-MUFA (low-carbohydrate) diet: 40% carbohydrates, 20% protein, 40% fat; B: High-complex-carbohydrate (low-fat) diet: 60% carbohydrates, 20% protein, 20% fat Medication: all had oral agents and/or insulin, 69% had hypertension and used diuretics, ACE inhibitors, calcium channel inhibitors	Fasting plasma glucose and HbA1c; fasting plasma cholesterol; fasting triglycerides, LDL, HDL	High risk (attrition bias 35%)
Lopez-Espinoza, 1984 (79) (not included in results; see Supplemental Table 4)	RCT (Oxford, UK)	59 (34 men/25 women); mean age: 56 y; T2D; BMI: 28.7–31.9	7 y A: Low-carbohydrate diet ($n = 25$); B: Modified-fat diet ($n = 34$) A: Low-carbohydrate diet: 40% carbohydrates; B: Modified-fat diet: 30% 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, crossover (Oxford, UK)	15 (sex not reported); age: 51–75 y; T2D; high doses of oral antiglycemic agents	6 wk (crossover) A: Low-carbohydrate diet; B: High-carbohydrate (low-fat), high-fiber diet No washout between diets A: Low-carbohydrate diet: 35% carbohydrates, 22% protein, 43% fat; B: High-carbohydrate (low-fat), high-fiber diet: 60% carbohydrates, 24% protein, 16% 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 y; T2D; BMI: 27	4 wk 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% carbohydrates, 25% protein, 35% fat; B: High-carbohydrate (low-fat) diet: 65% carbohydrates, 25% protein, 10% fat Exercise twice daily recommended (walking) No medication	Fasting plasma glucose; fasting plasma cholesterol, HDL, triglycerides; weight, body fat; measurement of visceral and subcutaneous fat mass	Unclear risk (selection bias, performance bias)
Ney, 1982 (82) (not included in results: see Supplemental Table 4)	RCT (San Diego, CA)	20 women; mean age: 26.6–32 y; type 1 diabetes and T2D; pregnant	14–18 wk A: Control (low-carbohydrate) diet ($n = 10$); B: High-carbohydrate (low-fat) diet ($n = 10$) Intensive dietary instructions A: Control (low-carbohydrate) diet: 40% carbohydrates, 20% protein, 40% fat; B: High-carbohydrate (low-fat) diet: 65% carbohydrates, 20% protein, 15% 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)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Nielsen, 2005 (83)	CCT (Karlshamn, Sweden)	31 (sex unclear); mean age: 57.1 y; obese; T2D; BMI: 34.2–36.1	6 mo A: Low-carbohydrate diet ($n = 16$); B: High-carbohydrate (low-fat) diet ($n = 15$) Diets were calorie restricted A: Low-carbohydrate diet: 20% carbohydrates, 30% protein, 50% fat; B: High-carbohydrate (low-fat) diet: 60% carbohydrates, 15% protein, 25% fat Regular daily exercise recommended Medication: in low-carbohydrate diet group: 11, insulin; 15, metformin; 5, sulfonylurea; in high-carbohydrate low-fat diet group: 6, insulin; 10, metformin; 5, sulfonylurea	Fasting plasma glucose; HbA1c; body weight; BMI	Serious risk (confounding bias)
Nuttall, 2012 (84)	RCT, crossover (Minnesota, MN)	9 men; mean age: 61 y; T2D; BMI: 31	5 wk (crossover) A: Low biologically available glucose (LoBAG; low-carbohydrate) diet; B: Control (low-fat) diet; 5-wk washout in between diets Food delivered Isocaloric diets, aiming stable weight A: Low biologically available glucose (LoBAG; low-carbohydrate) diet: 30% carbohydrates, 30% protein, 40% fat; B: Control (low-fat) diet: 55% carbohydrates, 15% protein, 30% fat Medication: oral antidiabetic treatment was discontinued; all other medication was continued	Total α amino acid nitrogen; individual specific amino acids; cortisol and glucagon; 24-h 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, prealbumin and albumin; body-composition data (weight, measurement of fat-free mass)	Unclear risk (performance bias)
Rodríguez-Villar, 2004 (85) (not included in results; see Supplemental Table 4)	RCT, crossover (Barcelona, Spain)	26 (13 men/13 women); mean age: 61 y; T2D; BMI: 28.3	6 wk (crossover) A: High-MUFA (low-carbohydrate) 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: 40% carbohydrates, 15% protein, 40% fat (not 100%); B: High-carbohydrate (low-fat) diet: 50% carbohydrates, 15% protein, 30% fat (not 100%) Medication: oral hypoglycemic medication	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 A-I	High risk (no washout)
Samaha, 2003 (86) (not included in results; see Supplemental Table 4)	RCT (Philadelphia, PA)	132 (109 men/23 women); mean age: 54 y; obese adults; BMI: 43–44	6 mo 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 carbohydrate/d; B: Low-fat diet: <30% fat and calorie restricted, 500 kcal/d 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%)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Saslow, 2017 (87) (not included in results; see Supplemental Table 4)	RCT, multicenter (USA)	25 (10 men/15 women); mean age: 56 y; T2D; weight: 90.9–109.7 kg	32 wk 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-carbohydrate diet group, participants were encouraged 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); CES-D; mDES; self-assessed physical symptoms with adapted Short Form health survey to measure of health-related quality of life, to assess vitality (energy and fatigue); Dietary Self-Report (My FitnessPal)	High risk (performance bias and attrition bias 28%)
Shah, 2005 (88) (not included in results; see Supplemental Table 4)	RCT, crossover, multicenter (USA)	42 (33 men/9 women); mean age: 58 y; T2D	6 wk (crossover) A: High-*cis*-monounsaturated-fat (low carbohydrate) diet (high-MUFA diet); B: High-carbohydrate (low-fat) diet 1-wk washout between diets Food prepared in metabolic kitchen, taken home, aim to maintain body weight A: High-MUFA diet: 40% carbohydrates, 15% protein, 45% fat; B: High-carbohydrate (low-fat) diet: 55% carbohydrates, 15% protein, 30% fat Maintain usual level of activity Medication: blood pressure medication kept stable, no information 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 y; BMI ≥27 or T2D	2 y A: Low-carbohydrate diet ($n = 109$); B: Low-fat diet ($n = 104$); C: Mediterranean diet ($n = 109$) Intensive support and follow-up by dietitian with a gradual increase after 2 mo to a maximum of 120 g per day to maintain the weight loss Only the low-fat and the Mediterranean diet were calorie restricted A: Low-carbohydrate diet: <20 g and later 120 carbohydrates; B: Low-fat diet: <30% fat Medication: 6–12% used oral antidiabetics	Weight; BMI; waist circumference; cholesterol, LDL, HDL, triglycerides; fasting plasma glucose/insulin; plasma high-sensitivity C-reactive protein; plasma high-molecular-weight adiponectin; plasma leptin; ;iver function tests; HOMA-IR; HbA1c in the diabetic patients (data for $n = 36$)	Unclear risk (selection bias, performance bias, attrition bias 11.5%)
Simpson, 1979 (90) (not included in results; see Supplemental Table 4)	RCT, crossover (Oxford, UK)	18 (15 men/3 women); mean age: 54 y; T2D	6 wk (crossover) A: Low-carbohydrate diet; B: High-carbohydrate (low-fat) diet No washout between diets Diets were isoenergetic A: Low-carbohydrate diet: 40% carbohydrates; B: High-carbohydrate (low-fat), high-fiber diet: 60% carbohydrates Medication: 14, sulfonylurea	Fasting plasma glucose; triglycerides HbA1c; cholesterol, HDL, LDL, VLDL; weight	High risk (attrition bias 22.2%, no washout)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Simpson, 1981 (91) (not included in results; see Supplemental Table 4)	RCT, crossover (Oxford, UK)	18 (10 men/8 women); mean age: 52.5 y; T2D	6 wk (crossover) A: Low-carbohydrate diet; B: High-carbohydrate (low-fat) diet No washout between diets Diets were isoenergetic A: Low-carbohydrate diet: 40% carbohydrates, 20% protein, 40% fat; B: High-carbohydrate (low-fat), high-fiber diet: 60% carbohydrates, 20% protein, 20% fat Medication: 14, sulfonylurea; 1 also taking 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, crossover (Oxford, UK)	10 (8 men/2 women); mean age: 58 y; T2D	4 wk (crossover) A: Low-carbohydrate diet; B: High-carbohydrate (low-fat) diet No washout between diets A: Low-carbohydrate diet: 35% carbohydrates, 20% protein, 45% fat; B: High-carbohydrate (low-fat), high-fiber diet: 60% carbohydrates, 20% protein, 20% 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 y; obese; T2D	24 wk A: Very-low-carbohydrate, high-unsaturated/low-saturated-fat diet ($n = 58$); B: High-unrefined-carbohydrate, lowfat diet ($n = 57$) Diets were isocaloric and calorie restricted Intensive support and follow-up by dietitians A: Very-low-carbohydrate diet: 14% carbohydrates, 28% protein, 58% fat; B: High-unrefined-carbohydrate, low-fat diet: 53% carbohydrates, 17% protein, <30% 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 article in 2018 (see Supplemental Table 5) 2-y data are reported
Walker, 1995 (94)	RCT, crossover (Geelong, Australia)	24 (9 men/15 women); mean age: 58.3 y; T2D; BMI: 28.8–29.1	3 mo (crossover) A: Modified-fat (low-carbohydrate) diet; B: High-carbohydrate (low-fat) diet 1-mo washout between diets Diets were isocaloric Regular follow-up by a dietitian A: Modified-fat (low-carbohydrate) diet: 40% carbohydrates, 14% protein, 36% fat; B: High-carbohydrate (low-fat) diet: 50% carbohydrates, 17% protein, 23% fat Medication: when necessary, low-dose hypoglycemic agents	Fasting plasma glucose/fasting plasma insulin; body weight/BMI; blood pressure; HbA1c; total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, VLDL cholesterol; free fatty acids; acceptance of the diets	Unclear risk (performance bias, and unclear how many initially randomized)
Ward, 1982 (95) (not included in results; see Supplemental Table 4)	RCT, crossover (Oxford, UK)	7 (sex not reported); mean age: 55 y; T2D	6 wk (crossover) A: Low-carbohydrate diet; B: High-carbohydrate (low-fat) diet No washout between diets Low-carbohydrate diet: 40% carbohydrates, 20% protein, 40% fat High-carbohydrate (low-fat) diet: 60% carbohydrates, 22% protein, 18% fat Medication: 4, oral hypoglycemic	Fasting plasma glucose/insulin; fasting blood for determination of monocyte insulin receptor binding	High risk (no washout)

(*Continued*)

TABLE 1 (*Continued*)

First author, year (ref)	Methods (location)	Participants	Interventions	Outcomes	Risk of bias
Wolever, 2008 (96)	RCT, multicenter (Canada)	162 (74 men, 88 women); mean age: 60 y; T2D; BMI: 30.1–31.6	1 y A: Low-carbohydrate, 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-MUFA diet: 39.3% carbohydrates, 20.6% protein, 40.1% fat (actual intake) High-carbohydrate, low-glycemic-index (low-fat) diet: 51.9% carbohydrates, 21.6% protein, 26.5% fat (actual intake) High-carbohydrate, high-glycemic-index (low-fat) diet: 46.5% carbohydrates, 22.7% protein, 30.8% fat (actual intake)	Fasting plasma glucose/fasting plasma insulin; HbA1c; serum cholesterol, triacylglycerol, apo A-I, and apoB, HDL cholesterol, LDL cholesterol; CRP; weight; waist circumference; systolic and diastolic blood pressure	Unclear risk (performance bias, attrition bias 19.8%), reporting bias); in follow-up article in 2017 (see Supplemental Table 5) quality-of-life data are reported
Yamada, 2014 (97)	RCT (Kitasato, Japan)	24 (12 men/12 women; mean age: 63 y; T2D; BMI: 24.5–27	6 mo 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/d; B: calorie-restricted (low-fat) diet: 50–60% carbohydrates, <20% protein, <25% fat Medication: not changed unless hypoglycemia occurred	HbA1c; fasting plasma glucose; body weight; incidence of hypoglycemic episodes; serum total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides; blood pressure; markers for atherosclerosis; renal function; liver enzymes; quality of life; patients completed the DTSQ and the PAID scale; adverse events	Unclear risk (performance bias, detection bias)

[1]See also Supplemental Table 6 for all details and an extensive version. ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; apo, apolipoprotein; CCT, controlled clinical trial; CES-D, Center for Epidemiological Studies–Depression Scale; CRP, C-reactive protein; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GHb = glycated hemoglobin; HbA1c, glycated hemoglobin; mDES, Modified Differential Emotions Scale; PAID, Problem Areas in Diabetes; RCT, randomized controlled trial; ref, reference; T2D, type 2 diabetes; %, percentage of energy.

wash-out period of ≥4 wk and provided data that we were able to include in the meta-analyses (78, 84, 94).

The data from 5 of the RCTs were unusable (see Supplemental Table 4). One study (79) did not address any of our outcomes, 1 study (82) did not provide separate data for patients with type 1 diabetes and T2D, 3 other studies (76, 86, 87) targeted our criteria of a low-carbohydrate compared with a low-fat diet (%) but appeared to subsequently exceed our cutoff values by >2% at follow-up. Furthermore, in the study by Samaha et al. (86), data are reported on some outcomes for diabetics (glucose, insulin, and HbA1c), but it is unclear how many diabetic patients remained in each intervention group throughout the study period. The report indicated that there was a 40% drop-out rate 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 that could be further analyzed and subsequently entered into the meta-analyses.

Our predefined outcomes were evaluated as follows—HbA1c (25 studies); plasma concentrations in the fasted condition: glucose (29 studies), triglycerides (31 studies), HDL cholesterol (30 studies), and LDL cholesterol (28 studies); body weight (23 studies); BMI (10 studies); waist circumference (7 studies); blood pressure (11 studies); and quality of life (5 studies).

Sources of funding were reported in all but 2 of the studies (78, 97). Declarations of conflicts of interest were only reported in 4 studies (72, 74, 87, 96), but we considered that either funding or conflicts of interest might have resulted in potential bias in 6 (72, 75, 90–92, 96) of the studies, in which 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 judgments in several of the risk-of-bias domains for 3 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 of a washout period) between diets in the crossover studies ($n = 13$) or a high drop-out rate ($n = 8$), or both and 1 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 judgments.)

The risk-of-bias assessments for the 3 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 Figures 1–3 (see also under "Statistical analysis" above). The robustness of our results was underpinned

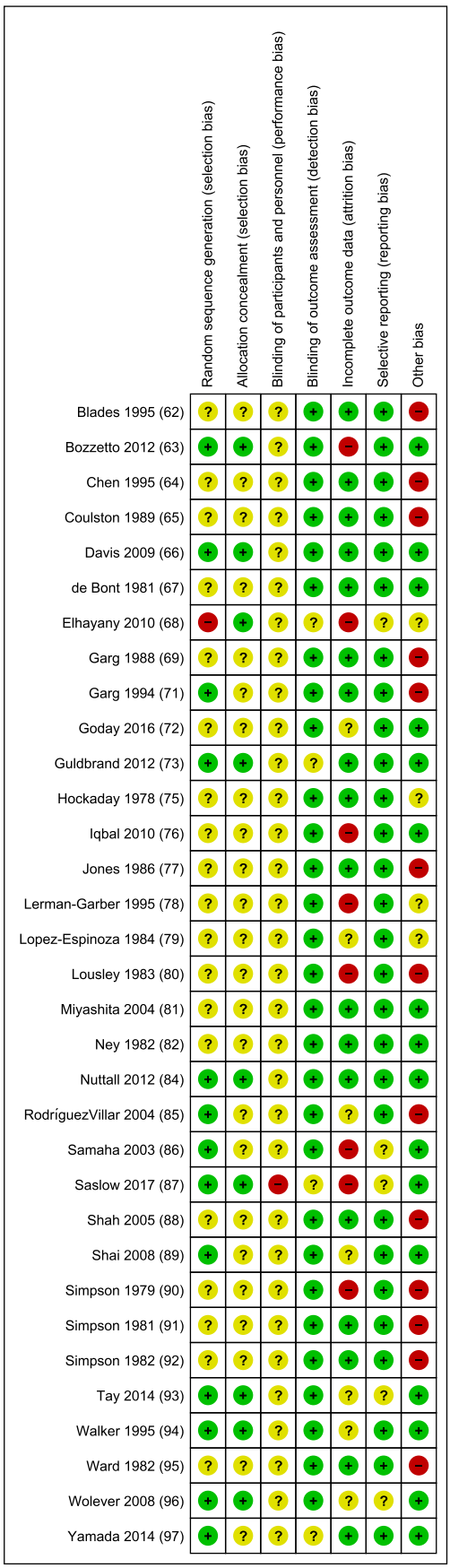

FIGURE 2 Risk-of-bias summary: review authors' judgments about each risk of bias item for each included randomized controlled trial. (+) Low risk of bias; (?) unclear risk of bias; (−) high risk of bias.

TABLE 2
Risk of bias using ROBINS-I for controlled clinical trials[1]

First author, year (ref)	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 results	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

[1] ref, reference; ROBINS-I, risk of bias in nonrandomised studies.

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 in 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 in 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 2 time windows, the low-carbohydrate diets induced a greater decrease in fasting glucose concentration than the low-fat diets (≥8–16 wk and ≥16–26 wk; moderate-certainty evidence).

Change from baseline in fasting triglyceride 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 toward an effect in favor of the low-carbohydrate data, only the data reported beyond 16 wk favored the low-carbohydrate diets (moderate- to high-certainty evidence).

Change from baseline in 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 cholesterol in favor of the low-carbohydrate diets (low- to moderate-certainty evidence), which persisted at 2 y, but the latter was based on data available from only 2 of the studies (73, 93).

Change from baseline in 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 shown between the 2 diet arms at any time point (moderate- to high-certainty evidence; see **Figure 7**).

Change from baseline in 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 kg) only at ≥8–16 wk in favor of low-carbohydrate food (high-certainty evidence).

Change from baseline in BMI

Seven studies evaluated the effect of the 2 diets on BMI over time (68, 72, 73, 83, 93, 94, 97). There was little to no difference between the 2 dietary approaches at the assessed time points (low- to high-certainty evidence; see **Supplemental Figure 5**).

Change from baseline in waist circumference

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

Change from baseline in 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 2 diets (low- to high-certainty evidence), except at 6 mo, where diastolic blood pressure probably declined more with low-carbohydrate food (MD: −1.91 mm Hg; 95% CI: −3.63, −0.18 mm Hg; see **Supplemental Figures 7** and **8**).

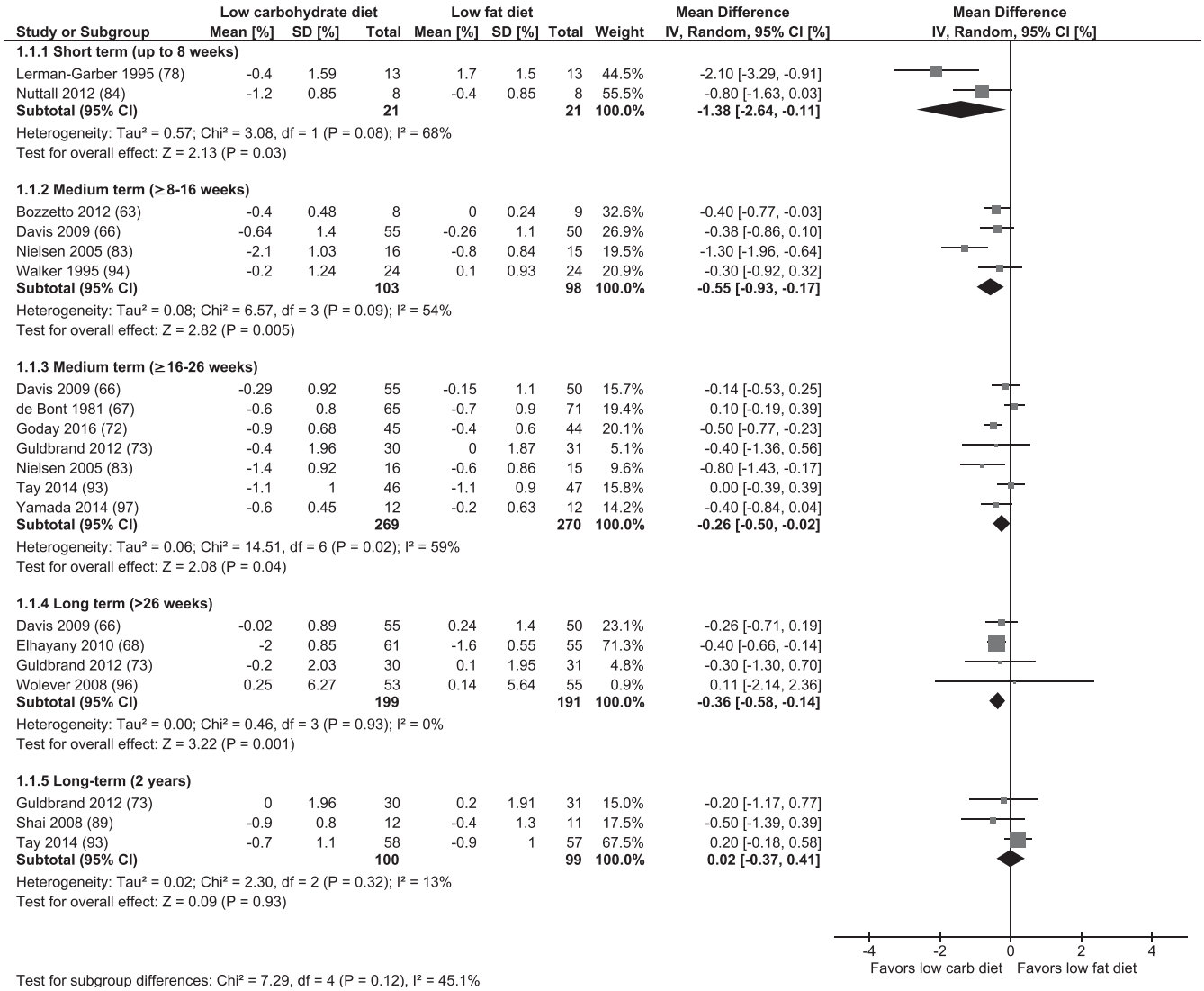

FIGURE 3 Change from baseline in HbA1c. The forest plot (the graph on the right-hand side) shows 1 line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the gray box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. carb, carbohydrate; HbA1c, glycated hemoglobin; IV, inverse variance.

Change from baseline in quality of life

Four studies provided data on quality of life (66, 73, 96, 97). The data in the study by Davis et al. (66) were reported in a subsequent article 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 with regard to 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 (<8 weeks)

The data up to 8 wk as well as the certainty of evidence are summarized in **Table 3**. However, because the possible causes of heterogeneity are not fully captured in this table, we provide details to accompany this and the following tables.

The substantial heterogeneity between studies for HbA1c is likely due to a significant increase in HbA1c in the high-carbohydrate (low-fat) group in the study by Lerman-Garber et al. (78), which may be attributable to the baseline imbalance of HbA1c, by the relatively high (60%) carbohydrate content of the high-carbohydrate diet, or both. Furthermore, consideration

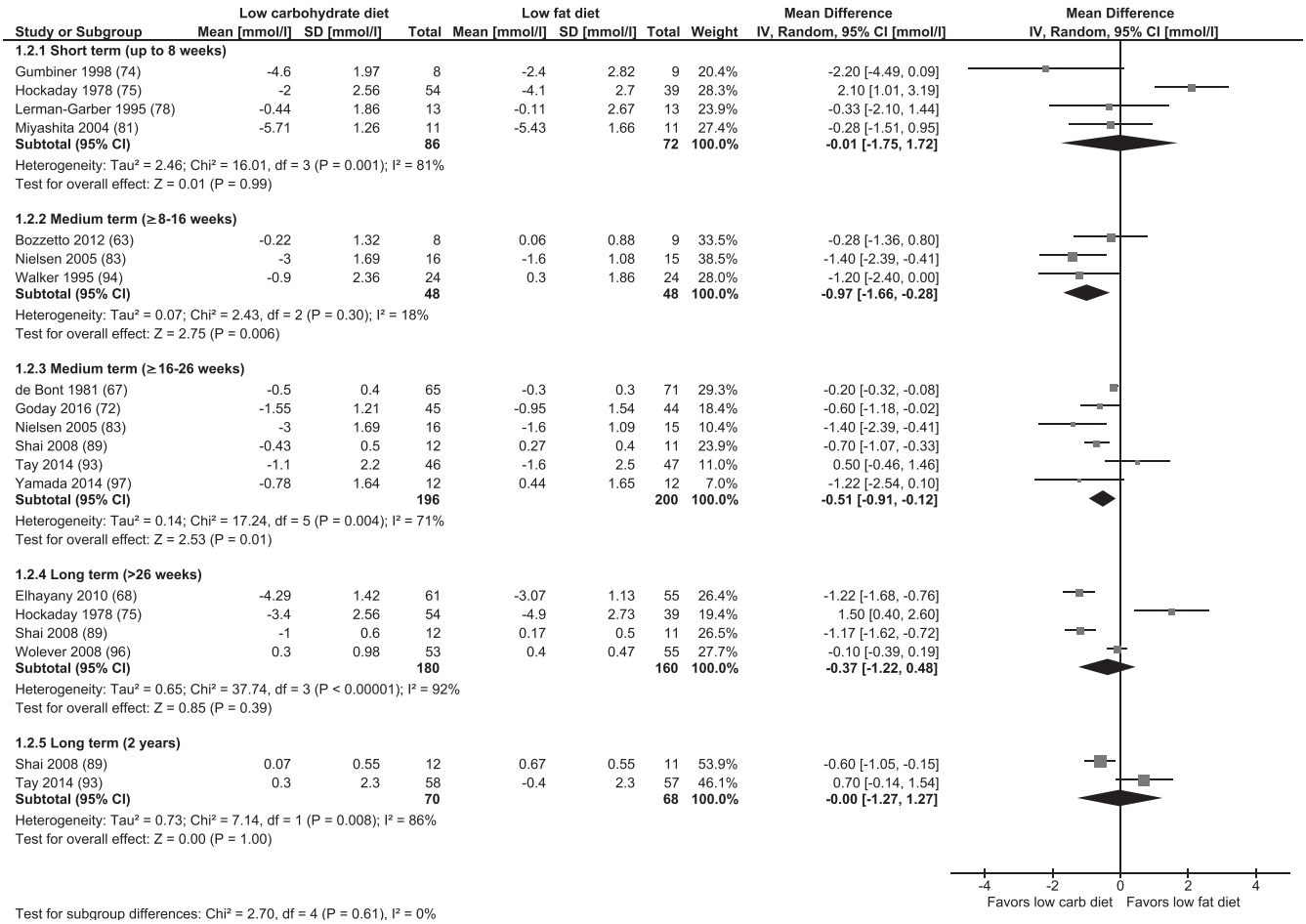

FIGURE 4 Change from baseline in fasting glucose. The forest plot (the graph on the right-hand side) shows 1 line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the gray box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. carb, carbohydrate; IV, inverse variance.

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 by Hockaday et al. (75), in which the low-fat-diet group did clearly better than the low-carbohydrate group. However, this may have been due to the fact that plasma glucose concentrations at baseline were substantially higher in the participants receiving the low-fat diet.

Heterogeneity between studies for fasting triglycerides was primarily caused by the study by Gumbiner et al. (74), which reported a considerable reduction in plasma triglyceride concentrations in participants following the low-carbohydrate diet. 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% from carbohydrate and 70% from fat, whereas the low-fat diet had 70% from carbohydrates and only 10% from fat. All of the other included studies had ±40% from carbohydrates in their low-carbohydrate 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 concentrations increased more in response to low-carbohydrate food in this study (even in the absence of effects on triglyceride concentrations) than the other included studies.

Medium-term measurements (≥8–16 wk)

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 on HbA1c was primarily caused by the study by Nielsen et al. (83). There was a larger reduction in HbA1c in this study than in the other 3 studies, probably because the carbohydrate content of the low-carbohydrate diet in this study was only 20%, as opposed to 30–40% in the other 3 studies. Moreover, this CCT was at serious risk of bias, because participants who were assigned to low-carbohydrate food were recruited via an informational 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 showed interest in their condition and in alternative dietary strategies, whereas participants in the control group were

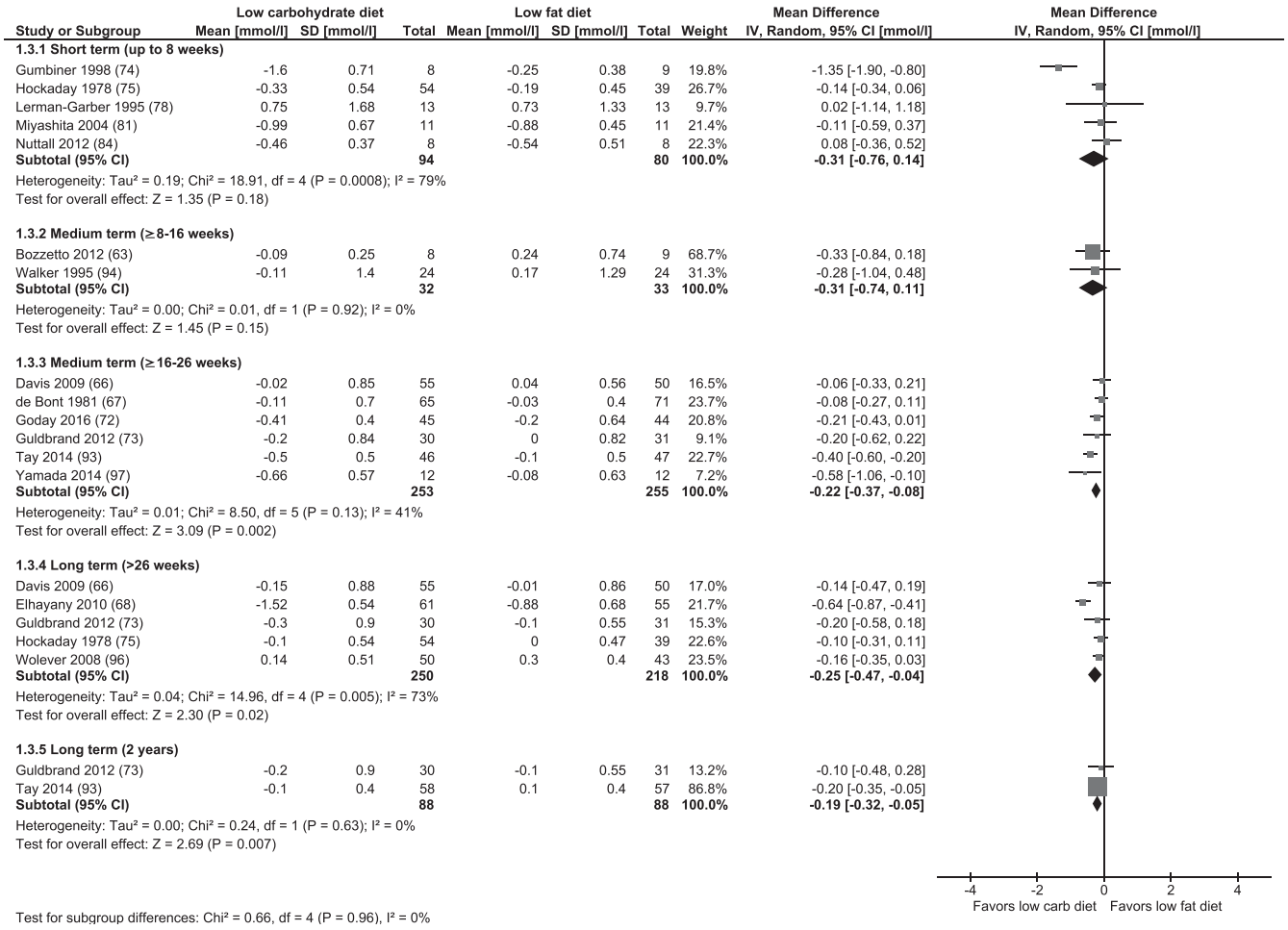

FIGURE 5 Change from baseline in fasting triglycerides. The forest plot (the graph on the right-hand side) shows 1 line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the gray box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. carb, carbohydrate; IV, inverse variance.

apparently less than interested. Affinity with or preference for a specific intervention is most likely to have an impact on the outcome.

With regard to change from baseline in BMI, 2 studies compared both low-carbohydrate and low-fat diets, but they were very different in other respects. The CCT (83), as just mentioned, had a serious risk of bias (see above), and the dietary interventions studied were calorie restricted and very low carbohydrate (20%), and participants were instructed to exercise 30 min/d. Conversely, in the study by Walker et al. (94), the low-carbohydrate intervention contained 40% from 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 with low-carbohydrate food in Davis et al. (66)] may have been caused by the fact that the % of carbohydrates of actual intake in the low-carbohydrate group at that time point was 24% in the study by Davis et al. (66) compared with 40% in Walker et al. (94).

Medium-term measurement (≥16–26 wk)

Data on the prespecified outcomes as well as the certainty of evidence for this time period are shown in **Table 5**. Heterogeneity between studies for HbA1c was caused by 2 of the studies (67, 93). The reductions in HbA1c in both of these were substantial in both diet arms, but it remains unclear why the difference in HbA1c reduction between low-carbohydrate and low-fat diets in these studies was relatively small. The participant characteristics, medications used (and discontinuance of medication during the study), dietary composition, or drop-out rate do not appear to differ significantly between studies. Tay et al. (93) reported a significant difference in favor of the low-carbohydrate intervention between the 2 diet groups in participants with a high HbA1c at baseline (>7.8%), but there was no difference between groups as a whole.

Heterogeneity between studies for fasting glucose was primarily caused by the same 2 studies (67, 93). It remains unclear why these studies differed from the other studies in terms of the response of fasting plasma glucose concentrations to dietary intervention.

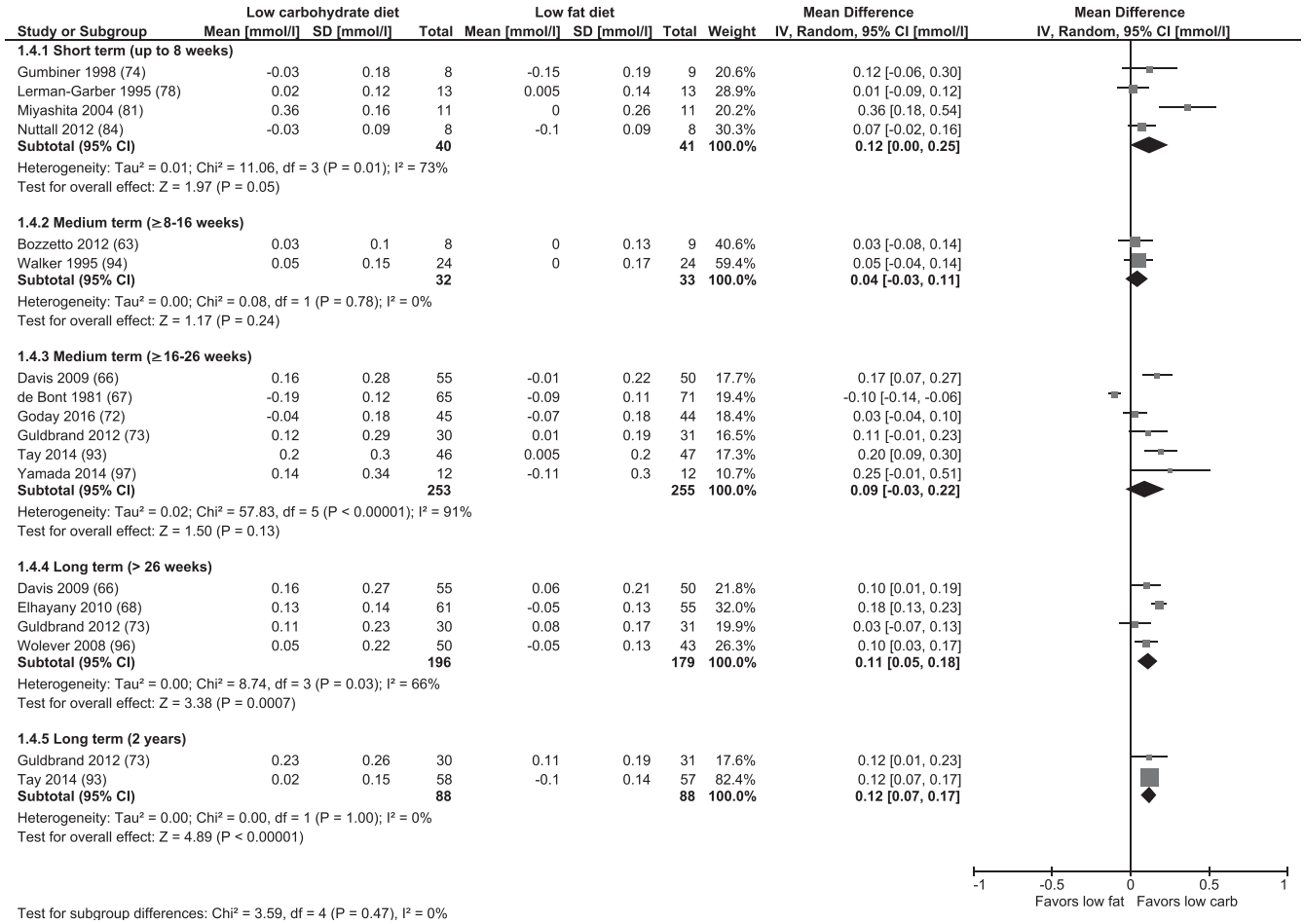

FIGURE 6 Change from baseline in fasting HDL cholesterol. The forest plot (the graph on the right-hand side) shows 1 line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the gray box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. carb, carbohydrate; IV, inverse variance.

The heterogeneity between studies for fasting HDL cholesterol was fully attributable to the slight reduction in HDL cholesterol in response to low-carbohydrate food in 2 of the studies (67, 72). This discordance in the data may be due to the relatively high baseline HDL-cholesterol concentrations in both studies, which paves the way for random changes (regression) toward a lower mean on subsequent measurement. We were unable to identify other differences between the included studies that might provide an explanation for the heterogeneity or variability in HDL-cholesterol concentrations in response to the dietary intervention.

For the outcome of change from baseline in body weight as well as BMI, heterogeneity was essentially caused by 2 of the studies (72, 83), which showed 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 participants in the low-carbohydrate diet group being presumably more adherent due to the counseling 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 fewer calories (600–800 kcal in the "active" phase) than the low-fat diet (500–1000 kcal restriction according to each individual's 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. (73) and Yamada et al. (97) reported 6-mo data on changes in quality of life, but used different measurement scales. Quality-of-life data from the study by Guldbrand et al. (73) were published in a subsequent article in 2014 (see Supplemental Table 5). Data were collected by using the generic Short Form–36 (SF-36), a 36-item questionnaire covering 8 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 6 by 23 patients in the low-carbohydrate group and by 22 in the low-fat intervention

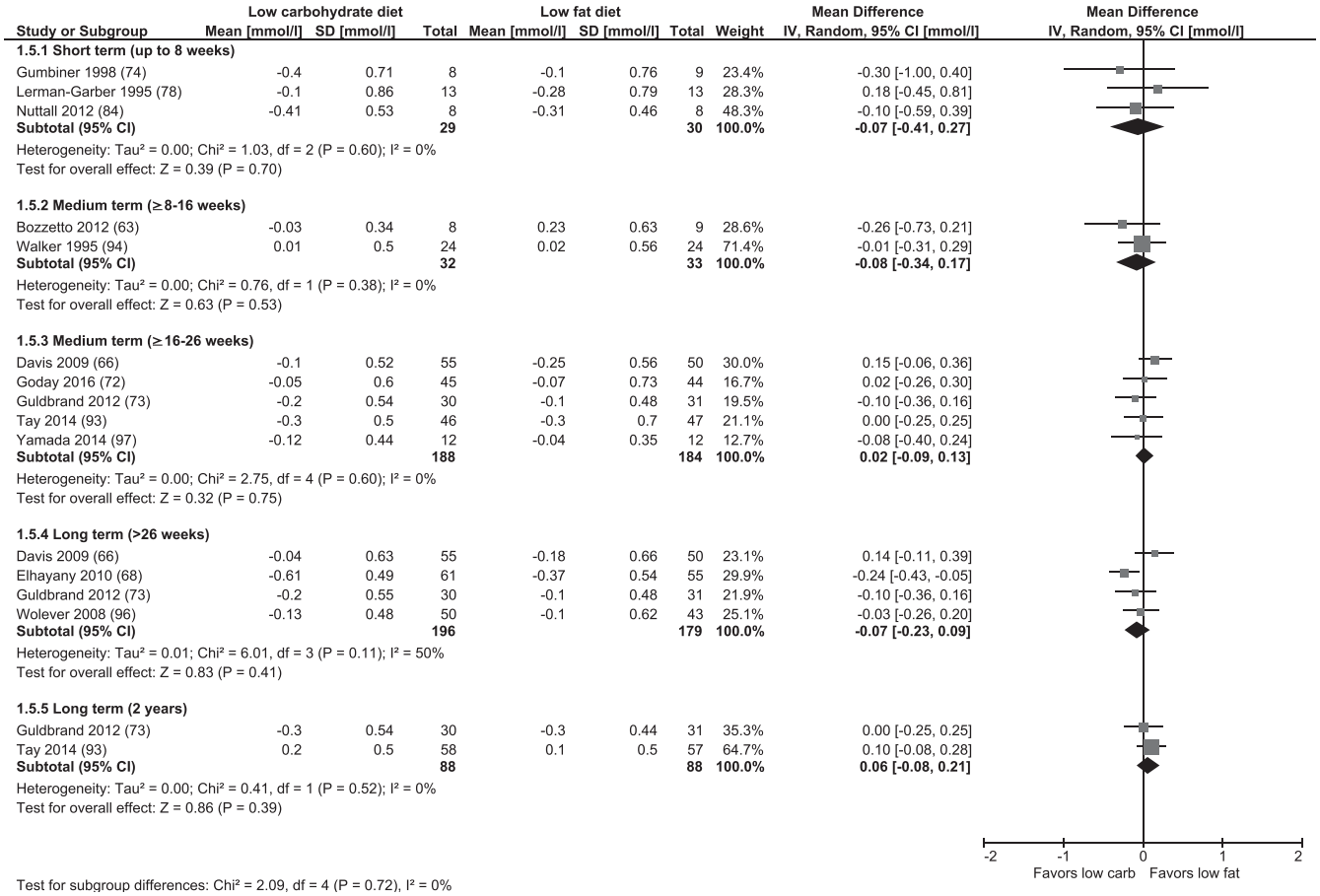

FIGURE 7 Change from baseline in fasting LDL cholesterol. The forest plot (the graph on the right-hand side) shows 1 line representing each study in the meta-analysis, plotted according to the mean difference (indicated by the gray box on each line). The black diamond at the bottom of each graph indicates the average effect size of the studies. carb, carbohydrate; IV, inverse variance.

group. The mean ± SD change from baseline in PCS at 6 mo was −0.90 ± 7.44 in the low-carbohydrate group compared with 0.50 ± 6.30 in the low-fat group. The mean ± SD change from baseline in MCS was −1.70 ± 8.43 in the low-carbohydrate diet group compared with 1.80 ± 6.30 in the low-fat group.

In the study by Yamada et al. (97), 2 different instruments were used: the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Problem Areas in Diabetes scale (PAID). The DTSQ measures treatment satisfaction in patients with diabetes and covers 6 satisfaction items on a 7-point Likert scale from 0 to 6, with a maximum 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 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 (± SD) increased from 24.0 ± 6.6 by 3.60 ± 3.98 at 6 mo in the 12 patients following a low-carbohydrate diet compared with an increase from 21.6 ± 3.3 by 3.10 ± 2.72 in the 12 patients following 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 (± SD) changed from 42.1 ± 13.5 by −4.30 ± 8.12 in the low-carbohydrate-diet group and from 57.8 ± 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 in fasting glucose was almost fully attributable to the differing results of 2 of the studies (75, 96). The beneficial effect of low-fat food in the study by Hockaday et al. (75) may have been biased by the higher glucose concentrations at baseline in the participants assigned to receive low-fat food. The relatively minor difference in fasting glucose concentrations in response to low-fat compared with 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

TABLE 3
Low-carbohydrate diet (≤40% carbohydrate) compared with low-fat diet (≤30% fat) for metabolic control in persons with type 2 diabetes: data up to 8 wk[1]

	Anticipated absolute effects				
Outcomes	Value with low-fat diet (≤30% fat)	Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies (refs)	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in HbA1c (follow-up—range: 4–5 wk)	The mean change from baseline in HbA1c ranged from −0.4% to 1.7%	The mean change from baseline in HbA1c in the low-carbohydrate group was 1.38% lower (−2.64%, −0.11%)	42; 2 RCTs (78, 84)	⊕◯◯◯ Very low[3–5]	A low-carbohydrate diet may reduce HbA1c more than a low-fat diet, but we are very uncertain; a difference of 0.5% in HbA1c is considered to be clinically important
Change from baseline in fasting glucose (follow-up—range: 4–6 wk	The mean change from baseline in fasting glucose ranged from −5.43 to −0.11 mmol/L	The mean change from baseline in fasting glucose in the low-carbohydrate group was 0.01 mmol/L lower (−1.75, 1.72)	158; 4 RCTs (74, 75, 78, 81)[6]	⊕⊕⊕◯ Moderate[7–9]	A low-carbohydrate diet probably results in little to no difference in reduction in fasting glucose compared with the low-fat diet; both diets had a potentially important impact on glucose concentrations in the fasting condition
Change from baseline in fasting triglycerides (follow-up—range: 4–6 wk)	The mean change from baseline in fasting triglycerides ranged from −0.88 to 0.73 mmol/L	The mean change from baseline in fasting triglycerides in the low-carbohydrate group was 0.31 mmol/L lower (−0.76, 0.14)	174; 5 RCTs (74, 75, 78, 81, 84)[6]	⊕⊕⊕◯ Moderate[7,10,11]	A low-carbohydrate diet probably results in little to no difference in reduction in fasting triglycerides compared with a low-fat diet
Change from baseline in fasting HDL (follow-up—range: 4–6 wk)	The mean change from baseline in fasting HDL ranged from −0.15 to 0.005 mmol/L	The mean change from baseline in fasting HDL in the low-carbohydrate group was 0.12 mmol/L higher (0, 0.25)	81; 4 RCTs (74, 78, 81, 84)[6]	⊕⊕◯◯ Low[7,12,13]	A low-carbohydrate diet may result in a small increase in fasting HDL compared with a low-fat diet
Change from baseline in fasting LDL (follow-up—range: 5–6 wk)	The mean change from baseline in fasting LDL ranged from −0.31 to −0.1 mmol/L	The mean change from baseline in fasting LDL in the low-carbohydrate group was 0.07 mmol/L lower (−0.41, 0.27)	59; 3 RCTs (74, 78, 84)[6]	⊕⊕⊕◯ Moderate [5,14]	A low-carbohydrate diet probably results in little to no difference in reduction in fasting LDL compared with a low-fat diet
Change from baseline in body weight (follow-up—range: 4–6 wk)	The mean change from baseline in body weight ranged from −8.3 to −0.2 kg	The mean change from baseline in body weight in the low-carbohydrate group was 0.81 kg lower (−2.11, 0.49)	174; 5 RCTs (74, 75, 78, 81, 84)[6]	⊕⊕⊕◯ Moderate[5,7]	A low-carbohydrate diet probably results in little to no difference in reduction in weight loss after 4–6 wk compared with a low-fat diet; both diets have considerable effects on body weight
Change from baseline in BMI, not measured	No study addressed change of BMI up to 8 wk after the start of the diets	—	—	—	We are uncertain about the effect of a low-carbohydrate diet compared with a low-fat diet on BMI
Change from baseline of waist circumference, not measured	No study addressed change of waist circumference up to 8 wk after the start of the diets	—	—	—	We are uncertain about the effect of a low-carbohydrate diet compared with a low-fat diet on waist circumference
Change from baseline in systolic blood pressure (follow-up—mean: 5 wk)	The mean change from baseline in systolic blood pressure was −6 mm Hg	The mean change from baseline in systolic blood pressure in the low-carbohydrate group was 2 mm Hg lower (−15.29, 11.29)	16; 1 RCT (84)	⊕⊕◯◯ Low[15]	A low-carbohydrate diet may result in little to no difference in reduction in systolic blood pressure compared with a low-fat diet; systolic blood pressure declines in both diets to a clinically meaningful extent

(*Continued*)

TABLE 3 (*Continued*)

Outcomes	Anticipated absolute effects: Value with low-fat diet (≤30% fat)	Anticipated absolute effects: Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies (refs)	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline of diastolic blood pressure (follow-up—mean: 5 wk)	The mean change from baseline in diastolic blood pressure was −5 mm Hg	The mean change from baseline in diastolic blood pressure in the low-carbohydrate group was 5 mm Hg higher (−1.67, 11.67)	16; 1 RCT (84)	⊕⊕◯◯ Low[15]	A low-carbohydrate diet may result in a small increase to no difference in diastolic blood pressure
Change from baseline in quality of life, not measured	No study addressed change in quality of life up to 8 wk after the start of the diets	—	—	—	We are uncertain about the effect of a low-carbohydrate diet compared with a low-fat diet on quality of life

[1]Method of analysis for all outcomes: random effect (inverse variance). CCT, controlled clinical trial; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; RCT, randomized controlled trial; ref, reference; %, percentage of energy. ⊕⊕⊕⊕, high; ⊕⊕⊕◯, moderate; ⊕⊕◯◯, low; ⊕◯◯◯, very low.

[2]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).

[3]Downgraded 1 level for serious risk of bias. One study had a 35% drop-out rate.

[4]Downgraded 1 level for serious inconsistency ($I^2 = 68\%$).

[5]Downgraded 1 level for serious imprecision, low total sample size.

[6]One CCT.

[7]We did not downgrade for risk of bias for the study at high risk of bias, because removing the study did not really alter the effect estimate.

[8]Downgraded 1 level for serious inconsistency ($I^2 = 81\%$).

[9]We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise reductions of <3 mmol/L are not considered to be important. Therefore, the effect estimate is rather precise.

[10]Downgraded 1 level for serious inconsistency ($I^2 = 79\%$).

[11]We did not downgrade for imprecision. We considered reductions of <1 mmol/L not to be important to patients. Therefore, the effect estimate is rather precise.

[12]Downgraded 1 level for serious inconsistency ($I^2 = 73\%$).

[13]Downgraded 1 level for serious imprecision. Low sample size and the lower boundary of the 95% CI included no effect.

[14]We did not downgrade for risk of bias of the CCT or the high drop-out rate of another study because removing these had no important effect on the effect estimate.

[15]Downgraded 2 levels for very serious imprecision. Very low sample size, wide CI.

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 in fasting triglycerides was fully attributable to the more substantial decrease in triglycerides in response to carbohydrate restriction in one of the studies (68). A possible explanation could be that baseline plasma triglyceride concentrations were substantially higher in this study than in any of the other included studies (elevated concentrations 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 in HDL-cholesterol concentrations in response to low-carbohydrate food in the study by Elhayany et al. (68), which is most likely explained by the considerable concomitant decline in plasma triglyceride concentrations achieved in that study. Reduction in circulating (VLDL) triglycerides limits the exchange of cholesteryl esters between HDL and VLDL particles and thereby increases HDL cholesterol.

Almost all of the heterogeneity between the studies of the meta-analysis for data on change from baseline in LDL cholesterol was caused by the data from 1 study (68), which reported diametrically opposing results (larger decline in LDL cholesterol in response to the low-carbohydrate diet). This difference is difficult to explain but may be due to the differences in sex distribution and ethnicity between participants. It may also reflect differences in diet quality between the studies. Elhayany et al. (68) compared low-carbohydrate, low-glycemic-index Mediterranean food with low-fat food according to the American Diabetes Association 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 that addressed quality of life at 1 and 2 y was Guldbrand et al. (73). At 12 mo, the mean ± SD change from baseline in the low-carbohydrate group ($n = 27$) for the PCS was 2.60 ± 6.50 and 0.60 ± 6.32 in the low-fat group ($n = 28$) and for the MCS was 0.90 ± 4.34 compared with 1.10 ± 6.11. At

TABLE 4
Low-carbohydrate diet (≤40% carbohydrate) compared with low-fat diet (≤30% fat) for metabolic control in persons with type 2 diabetes: data for ≥8–16 wk[1]

	Anticipated absolute effects				
Outcomes	Value with low-fat diet (≤30% fat)	Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies (refs)	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in HbA1c (follow-up—range: 8–16 wk)	The mean change from baseline in HbA1c ranged from −0.8% to 0.1%	The mean change from baseline in HbA1c in low-carbohydrate group was 0.55% lower (−0.93%, −0.17%)	201; 4 RCTs (63, 66, 83, 94) [3]	⊕⊕◯◯ Low[4–6]	A low-carbohydrate diet may reduce HbA1c slightly compared with a low-fat diet; a difference of 0.5% of HbA1c is considered to be clinically important
Change from baseline in fasting glucose (follow-up—range: 8–16 wk)	The mean change from baseline in fasting glucose ranged from −1.6 to 0.3 mmol/L	The mean change from baseline in fasting glucose in the low-carbohydrate group was 0.97 mmol/L lower (−1.66, −0.28)	96; 3 RCTs (63, 83, 94)[3]	⊕⊕⊕◯ Moderate[7,8]	A low-carbohydrate diet probably results in a small effect that may not be an important reduction in fasting glucose compared with a low-fat diet
Change from baseline in fasting triglycerides (follow-up—range: 8–16 wk)	The mean change from baseline in fasting triglycerides ranged from 0.17 to 0.24 mmol/L	The mean change from baseline in fasting triglycerides in the low-carbohydrate group was 0.31 mmol/L lower (−0.74, 0.11)	65; 2 RCTs (63, 94)	⊕⊕⊕◯ Moderate[8,9]	A low-carbohydrate diet probably results in little to no difference in reduction in fasting triglycerides compared with a low-fat diet
Change from baseline in fasting HDL (follow-up—range: 8–16 wk)	The mean change from baseline in fasting HDL was 0 mmol/L	The mean change from baseline in fasting HDL in the low-carbohydrate group was 0.04 mmol/L higher (−0.03, 0.11)	65; 2 RCTs (63, 94)	⊕⊕⊕◯ Moderate[8,9]	A low-carbohydrate diet probably results in little to no difference in reduction in fasting HDL compared with a low-fat diet
Change from baseline in fasting LDL (follow-up—range: 8–16 wk)	The mean change from baseline in fasting LDL ranged from 0.02 to 0.23 mmol/L	The mean change from baseline in fasting LDL in the low-carbohydrate group was 0.08 mmol/L lower (−0.34, 0.17)	65; 2 RCTs (63, 94)	⊕⊕⊕◯ Moderate[8,9]	A low-carbohydrate diet probably results in little to no difference in reduction in fasting LDL compared with a low-fat diet
Changes from baseline in body weight (follow-up—range: 8–16 wk)	The mean changes from baseline in body weight ranged from −3.2 to 0 kg	The mean changes from baseline in body weight in the low-carbohydrate group was 2.04 kg lower (−3.23, 0.85)	201; 4 RCTs (63, 66, 83, 94)[3]	⊕⊕⊕⊕ High[7,10]	A low-carbohydrate diet results in a small effect that may not be an important reduction in body weight compared with a low-fat diet
Change from baseline in BMI (follow-up—range: 8–16 wk)	The mean change from baseline in BMI (kg/m^2) ranged from −0.7 to −0.3	The mean change from baseline in BMI in the low-carbohydrate group was 1.19 lower (−3.34, 0.96)	79; 2 RCTs (83, 94)[3]	⊕◯◯◯ Very low[11–13]	We are uncertain about the effect of a low-carbohydrate diet in reducing BMI compared with a low-fat diet
Change from baseline in waist circumference (follow-up—mean: 8 wk)	The mean change from baseline in waist circumference was 1 cm	The mean change from baseline in waist circumference in the low-carbohydrate group was 2 cm lower (−6.29, 2.29)	17; 1 RCT (63)	⊕⊕◯◯ Low[14]	A low-carbohydrate diet may result in little to no difference in reduction in waist circumference compared with a low-fat diet
Change from baseline in systolic blood pressure (follow up—mean: 16 wk)	The mean change from baseline in systolic blood pressure ranged from −1 to −0.98 mm Hg	The mean change from baseline in systolic blood pressure in the low-carbohydrate group was 0.64 mm Hg lower (−7.15, 5.78)	153; 2 RCTs (66, 94)	⊕⊕◯◯ Low[15]	A low-carbohydrate diet may result in little to no difference in reduction in systolic blood pressure compared with a low-fat diet
Change from baseline in diastolic blood pressure (follow up—mean: 16 wk)	The mean change from baseline in diastolic blood pressure ranged from −1 to −0.4 mm Hg	The mean change from baseline in diastolic blood pressure in the low-carbohydrate group was 0.82 mm Hg lower (−4.06, 2.42)	153; 2 RCTs (66, 94)	⊕⊕◯◯ Low[15]	A low-carbohydrate diet may result in little to no difference in reduction in diastolic blood pressure compared with a low-fat diet

(*Continued*)

TABLE 4 (*Continued*)

Outcomes	Anticipated absolute effects: Value with low-fat diet (≤30% fat)	Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies (refs)	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in quality of life, not measured	No study addressed change in quality of life up from 8 to 16 wk after the start of the diets	—	—	—	We are uncertain about the effect of a low-carbohydrate diet compared with a low-fat diet on quality of life

[1]Method of analysis for all outcomes: random effect (inverse variance). CCT, controlled clinical trial; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; RCT, randomized controlled trial; ref, reference; %, percentage of energy.

[2]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).

[3]One CCT.

[4]Downgraded 1 level for serious risk of bias. One RCT was at high risk of bias, and the CCT was at serious risk of bias

[5]We did not downgrade for inconsistency because the CIs were overlapping and I^2 was just 54%.

[6]Downgraded 1 level for imprecision. Upper boundary is not clinically important.

[7]We did not downgrade for risk of bias for the study at high risk of bias and the CCT at serious risk of bias, because removing these studies did not really alter the effect estimate.

[8]Downgraded 1 level for serious imprecision, low total sample size.

[9]We did not downgrade for risk of bias for the study at high risk of bias because removing the study did not really alter the effect estimate.

[10]We did not downgrade for imprecision. Although the minimal important difference is not established, we consider a reduction of <5% to be not important. Therefore, the effect estimate is rather precise.

[11]Downgrading 1 level for serious risk of bias. The CCT was at serious risk of bias.

[12]Downgraded 1 level for serious inconsistency ($I^2 = 94\%$).

[13]Downgraded 1 level for serious imprecision. Low sample size and the 95% CI included both benefit of the low-carbohydrate diet and no difference between the diets.

[14]Downgraded 2 levels for very serious imprecision. Very low sample size and the 95% CI included both benefit of the low-carbohydrate diet and no difference between the diets.

[15]Downgraded 2 levels for very serious imprecision. The 95% CI included both appreciable harm and benefit.

2 y, the change from baseline in the PCS for the low-carbohydrate group ($n = 25$) was -2.70 ± 8.49 compared with -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 the MCS, the changes from baseline were 1.40 ± 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 RCTs and CCTs (including 2161 patients) is the first, to our knowledge, to comprehensively and specifically compare the effects of low-carbohydrate with low-fat food on glucose control, the plasma lipid cardiovascular risk profile, and body weight of persons with T2D. Our results suggest that there is, in general, little to no difference between the metabolic effects of diets containing ≤40% from carbohydrates ("low carb") and diets containing ≤30% from fat ("low fat"). A low-carbohydrate diet may reduce HbA1c compared with a low-fat diet, particularly in the short and medium term up to 1 y, but we are uncertain about this effect. At 2 y, the difference between the effects of either diet on HbA1c had disappeared. The fact that all metabolic measurements tended to return to baseline values in both groups after 2 y suggests that lack of compliance with dietary prescriptions may have played a role. Although carbohydrate restriction more clearly improves other metabolic variables at many of the prespecified 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. Because the minimal clinically important difference for most of these metabolic variables has not been determined, our inference with regard to clinical meaning is arguable.

Both dietary strategies similarly affected LDL-cholesterol concentrations, which may come as a surprise, because (some) SFAs tend to increase LDL-cholesterol concentrations. However, this is particularly true if dietary PUFAs are substituted by SFAs. Substitution of carbohydrates by saturated fat has less of an effect on LDL-cholesterol concentrations (100). Blood pressure response (systolic as well as diastolic) was also not significantly different, although low-carbohydrate 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 body weight or waist circumference. There may be no important improvement in quality of life in response to either dietary strategy in the few studies assessing this outcome. The certainty of evidence for the secondary outcomes varied from very low to high, but is predominantly low at the various time points.

TABLE 5
Low-carbohydrate diet (≤40% carbohydrate) compared with low-fat diet (≤30% fat) for metabolic control in persons with type 2 diabetes: data for ≥16–26 wk[1]

	Anticipated absolute effects				
Outcomes	Value with low-fat diet (≤30% fat)	Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies (refs)	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in HbA1c (follow-up—range: 16–26 wk)	The mean change from baseline in HbA1c ranged from −1.1% to 0%	The mean change from baseline in HbA1c in the low carb group was 0.26% lower (−0.5, −0.02)	539; 7 RCTs (66, 67, 72, 73, 83, 93, 97)[3]	⊕⊕⊕◯ Moderate[4,5]	A low-carbohydrate diet probably results in a small effect that may not be an important reduction in HbA1c compared with a low-fat diet
Change from baseline in fasting glucose (follow-up—range: 16–26 wk)	The mean change from baseline in fasting glucose ranged from −1.6 to 0.44 mmol/L	The mean change from baseline in 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)[3]	⊕⊕⊕◯ Moderate[4,6,7]	A low-carbohydrate diet probably results in a small effect that may not be an important reduction in fasting glucose compared with a low-fat diet
Change from baseline in fasting triglycerides (follow-up—range: 16–26 wk)	The mean change from baseline in fasting triglycerides ranged from −0.2 to 0.04 mmol/L	The mean change from baseline in 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[8]	A low-carbohydrate diet results in a small effect that may not be an important reduction in fasting triglycerides compared with a low-fat diet
Change from baseline in fasting HDL (follow-up—range: 16–26 wk)	The mean change from baseline in fasting HDL ranged from −0.11 to −0.01 mmol/L	The mean change from baseline in 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[9,10]	A low-carbohydrate diet may result in little to no difference in increase in fasting HDL compared with a low-fat diet
Change from baseline in fasting LDL (follow-up—range: 16–26 wk)	The mean change from baseline in fasting LDL ranged from −0.3 to −0.04 mmol/L	The mean change from baseline in 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[11]	A low-carbohydrate diet results in little to no difference in changes in fasting LDL compared with a low-fat diet
Change from baseline in body weight (follow-up—range: 16–26 wk)	The mean change from baseline in body weight ranged from −11.5 to −1.4 kg	The mean change from baseline in 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)[3]	⊕⊕◯◯ Low[4,12,13]	A low-carbohydrate diet may result in little to no difference in reduction in body weight compared with a low-fat diet; both diets have considerable effects on body weight
Change from baseline in BMI (follow-up—range: 16–26 wk)	The mean change from baseline in BMI (kg/m^2) ranged from −4 to −0.6	The mean change from baseline in BMI in the low carb group was 1.48 kg/m2 lower (−3.45, 0.49)	298; 5 RCTs (72, 73, 83, 93, 97)[3]	⊕⊕◯◯ Low[4,14,15]	A low-carbohydrate diet may result in little to no difference in reduction in BMI compared with a low-fat diet; both diets have considerable effects on BMI
Change from baseline in waist circumference (follow-up—range: 16–26 wk)	The mean change from baseline in waist circumference ranged from −9.1 to −4 cm	The mean change from baseline in waist circumference in the low carb group was 2.98 cm lower (−7.14, 1.18)	243; 3 RCTs (72, 73, 93)	⊕⊕⊕◯ Moderate[15,16]	A low-carbohydrate diet probably results in little to no difference in reduction in waist circumference compared with a low-fat diet; both diets have considerable effects on waist circumference
Change from baseline in systolic blood pressure (follow-up—mean: 26 wk)	The mean change from baseline in systolic blood pressure ranged from −8.7 to −0.37 mm Hg	The mean change from baseline in 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[17]	A low-carbohydrate diet results in little to no difference in reduction in systolic blood pressure compared with a low-fat diet; the reduction in systolic blood pressure is clinically meaningful with both dietary interventions

(*Continued*)

TABLE 5 (*Continued*)

Outcomes	Anticipated absolute effects: Value with low-fat diet (≤30% fat)	Anticipated absolute effects: Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies (refs)	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in diastolic blood pressure (follow-up—mean: 26 wk)	The mean change from baseline in diastolic blood pressure ranged from −6.4 to 0.95 mm Hg	The mean change from baseline in diastolic blood pressure in the intervention group was 1.91 mmHg lower (−3.63, −0.18)	283; 4 RCTs (66, 73, 93, 97)	⊕⊕⊕◯ Moderate[5]	A low-carbohydrate diet probably results in a small effect that may not be an important reduction in diastolic blood pressure compared with a low-fat diet; the effect of both diets on diastolic blood pressure is of potential clinical significance
Change from baseline in quality of life (follow-up—mean: 26 wk)	In Guldbrand 2012 (73) the Short Form-36 was used, and in Yamada 2014 (97) the DTSQ and the PAID were used; but there was no difference in improvement in quality of life between the 2 diet groups with either of these instruments		69; 2 RCTs (73, 97)	⊕⊕◯◯ Low[18]	A low-carbohydrate diet may result in little to no difference in improvement in quality of life compared with a low-fat diet

[1]Method of analysis for all outcomes: random effect (inverse variance). CCT, controlled clinical trial; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; HbA1c, glycated hemoglobin; PAID, Problem Areas in Diabetes; RCT, randomized controlled trial; ref, reference; %, percentage of energy.

[2]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).

[3]One CCT.

[4]We did not downgrade for risk of bias for the CCT at serious risk of bias, because removing the study did not really alter the effect estimate.

[5]Downgraded 1 level for serious imprecision; the upper boundary of the CI is close to the line of no difference, although the lower boundary of the CI indicates a clinically important difference.

[6]Downgraded 1 level for serious inconsistency ($I^2 = 71\%$).

[7]We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise, reductions of <3 mmol/L are is not considered to be important. Therefore, the effect estimate is rather precise.

[8]We did not downgrade for imprecision. We considered reductions of <1 mmol/L not to be important to patients. Therefore, the effect estimate is rather precise.

[9]Downgraded 1 level for serious inconsistency ($I^2 = 91\%$).

[10]Downgraded 1 level for serious imprecision. The 95% CI includes both benefit of the low-carbohydrate diet and no difference between the diets. We considered an increase of 0.1 mmol/L to be important

[11]We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise, reductions of <1 mmol/L are not considered to be important. Therefore, the effect estimate is rather precise.

[12]Downgraded 1 level for serious inconsistency ($I^2 = 88\%$).

[13]Downgraded 1 level for serious imprecision. The 95% CI includes both benefit of the low-carbohydrate diet and no difference between the diets. We considered a reduction of 5% to be important (5–10 kg in most studies).

[14]Downgraded 1 level for serious inconsistency ($I^2 = 94\%$).

[15]Downgraded 1 level for serious imprecision. The 95% CI includes both benefit of the low-carbohydrate diet and no difference between the diets.

[16]We did not downgrade for inconsistency. Although $I^2 = 82\%$, the 95% CIs overlap, and we already downgraded for imprecision and decided not to downgrade twice.

[17]We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise, reductions of <4 mm Hg are not considered important. Therefore, the effect estimate is rather precise.

[18]Downgraded 2 levels for very serious imprecision, very low sample size.

Although all measurable differences between the metabolic effects of low-carbohydrate diets and those of low-fat diets were in favor of low-carbohydrate food, they were small, of uncertain clinical importance, and supported by only low- to moderate-certainty evidence according to GRADE. These observations are counterintuitive, because 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 methodologic heterogeneity between 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%) may have also played a role. However, the results of 3 studies comparing very-low-carbohydrate 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,

TABLE 6
Low-carbohydrate diet (≤40% carbohydrate) compared with low-fat diet (≤30% fat) for metabolic control in persons with type 2 diabetes: data for >26 wk[1]

	Anticipated absolute effects				
Outcomes	Value with low-fat diet (≤30% fat)	Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in HbA1c (follow-up—mean: 52 wk)	The mean change from baseline in HbA1c ranged from −1.6% to 0.24%	The mean change from baseline in HbA1c in the low-carbohydrate group was 0.36% lower (−0.58%, −0.14%)	390; 4 RCTs (66, 68, 73, 96)	⊕⊕◯◯ Low[3,4]	A low-carbohydrate diet may result in a small effect that may not be an important reduction in HbA1c compared with a low-fat diet
Change from baseline in fasting glucose (follow-up—mean: 52 wk)	The mean change from baseline in fasting glucose ranged from −4.9 to 0.4 mmol/L	The mean change from baseline in fasting glucose in the low-carbohydrate group was 0.37 mmol/L lower (−1.22, 0.48)	340; 4 RCTs (68, 75, 89, 96)	⊕⊕⊕◯ Moderate[5–7]	A low-carbohydrate diet probably results in little to no difference in changes in fasting glucose compared with a low-fat diet; both diets had a potentially important impact on glucose concentrations
Change from baseline in fasting triglycerides (follow-up—mean: 52 wk)	The mean change from baseline in fasting triglycerides ranged from −0.88 to 0.3 mmol/L	The mean change from baseline in fasting triglycerides in the low-carbohydrate group was 0.25 mmol/L lower (−0.47, −0.04)	468; 5 RCTs (66, 68, 73, 75, 96)	⊕⊕⊕◯ Moderate[5,8,9]	A low-carbohydrate diet probably results in a small effect that may not be an important reduction in fasting triglycerides compared with a low-fat diet
Change from baseline in fasting HDL cholesterol (follow-up—mean: 52 wk)	The mean change from baseline in fasting HDL cholesterol ranged from −0.05 to 0.08 mmol/L	The mean change from baseline in fasting HDL cholesterol in the low-carbohydrate group was 0.11 mmol/L higher (0.05, 0.18)	375; 4 RCTs (66, 68, 73, 96)	⊕⊕◯◯ Low[3,10,11]	A low-carbohydrate diet may increase fasting HDL cholesterol slightly compared with a low-fat diet
Change from baseline in fasting LDL (follow-up—mean: 52 wk)	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[5,12]	A low-carbohydrate diet results in little to no difference in reduction in fasting LDL compared with a low-fat diet
Change from baseline in body weight (follow-up—mean: 52 wk)	The mean change from baseline in body weight ranged from −7.6 to 2.8 kg	The mean change from baseline in body weight in the low-carbohydrate group was 0.19 kg lower (−1.65, 1.27)	483; 5 RCTs (66, 68, 73, 75, 96)	⊕⊕⊕⊕ High[5,13]	A low-carbohydrate diet results in little to no difference in reduction in body weight compared with a low-fat diet
Change from baseline in BMI (follow-up—mean: 52 wk)	The mean change from baseline in BMI (kg/m^2) ranged from −2.8 to −1.2	The mean change from baseline in BMI in the low-carbohydrate group was 0.38 lower (−1.03, 0.27)	177; 2 RCTs (68, 73)	⊕⊕⊕◯ Moderate[3,14]	A low-carbohydrate diet probably results in little to no difference in reduction in BMI compared with a low-fat diet
Change from baseline in waist circumference (follow-up—mean: 52 wk)	The mean change from baseline in waist circumference ranged from −9.1 to 6.6 cm	The mean change from baseline in waist circumference in the low-carbohydrate group was 0.79 cm lower (−2.73, 1.15)	285; 3 RCTs (68, 73, 96)	⊕⊕⊕⊕ High[5,14]	A low-carbohydrate diet results in little to no difference in reduction in waist circumference compared with a low-fat diet
Change from baseline in systolic blood pressure (follow-up—mean: 52 wk)	The mean change from baseline in systolic blood pressure ranged from −10 to 5 mm Hg	The mean change from baseline in systolic blood pressure in the low-carbohydrate group was 0.77 mm Hg higher (−3.68, 5.21)	274; 3 RCTs (66, 73, 96)	⊕⊕⊕◯ Moderate[15]	A low-carbohydrate diet probably results in little to no difference in change in systolic blood pressure compared with a low-fat diet
Change from baseline in diastolic blood pressure (follow-up—mean: 52 wk)	The mean change from baseline in diastolic blood pressure ranged from −8 to −1 mm Hg	The mean change from baseline in diastolic blood pressure in the low-carbohydrate group was 0.08 mm Hg lower (−2.56, 2.39)	274; 3 RCTs (66, 73, 96)	⊕⊕◯◯ Low[16]	A low-carbohydrate diet may result in little to no difference in change in diastolic blood pressure compared with a low-fat diet

(*Continued*)

TABLE 6 (*Continued*)

Outcomes	Anticipated absolute effects: Value with low-fat diet (≤30% fat)	Anticipated absolute effects: Difference between low-carbohydrate diet (≤40% carbohydrate) and low-fat diet (95% CI)	No. of participants and studies	Certainty of the evidence (GRADE)[2]	Comments
Change from baseline in quality of life; Assessed with Short Form-36 (follow-up—mean: 52 wk)	The MD for PCS was 2.00 (95% CI: −1.39, 5.39; $P = 0.25$) and for the MCS was 0.90 (SD: 4.34) vs. 1.10 (SD: 6.11) with an MD of −0.20 (95% CI: −2.99, 2.59; $P = 0.89$).		55; 1 RCT (73)	⊕⊕◯◯ Low[17]	A low-carbohydrate diet may result in little to no difference in change in quality of life compared with a low-fat diet

[1]Method of analysis for all outcomes: random effect (inverse variance). GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; MCS, mental component score; MD, mean difference; PCS, physical component score; RCT, randomized controlled trial; ref, reference; %, percentage of energy.

[2]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).

[3]Downgraded 1 level for serious risk of bias. One study was at high risk of bias and removing this study did alter the effect estimate.

[4]Downgraded 1 level for serious imprecision. The upper boundary of the CI was not clinically important.

[5]We did not downgrade for risk of bias for the study at high risk of bias, because removing the study did not really alter the effect estimate.

[6]Downgraded 1 level for serious inconsistency ($I^2 = 92\%$).

[7]We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise, reductions of <3 mmol/L are not considered to be important. Therefore, the effect estimate is rather precise.

[8]Downgraded 1 level for serious inconsistency ($I^2 = 73\%$).

[9]We did not downgrade for imprecision. We considered reductions of <1 mmol/l not to be important to patients. Therefore, the effect estimate is rather precise and the CI does not include appreciable benefit or harm.

[10]We did not downgrade for inconsistency, because we already downgraded for risk of bias and imprecision.

[11]Downgraded 1 level for serious imprecision. The 95% CI also included no appreciable benefit.

[12]We did not downgrade for imprecision. Although the minimal important difference is not established, based on clinical expertise, reductions of <1 mmol/L are not considered to be important. Therefore, the effect estimate is rather precise.

[13]We did not downgrade for imprecision. The 95% CI did not include appreciable harm or benefit. We considered a reduction of 5% to be important (5–10 kg in most studies).

[14]We did not downgrade for imprecision. The 95% CI did not include appreciable harm of benefit.

[15]Downgraded 1 level for serious imprecision. The CI included appreciable harm.

[16]Downgraded 2 levels for very serious imprecision. The 95% CI included both appreciable benefit and harm.

[17]Downgraded 2 levels for very serious imprecision. Very low sample size and wide CI.

which enabled the answering of a clearly defined clinical question on the comparison of 2 explicit dietary strategies for management of T2D. Any methodologic 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 methodologic 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-carbohydrate interventions were indeed very low (<20%) in carbohydrate (72, 74, 93), whereas others were only mildly restrictive, and previous reports suggest that HbA1c declines in proportion to the energy percentage of carbohydrates in the diet (10). Similarly, in some studies (74, 81), the fat content of the low-fat intervention was much lower (<15%) than in others. Moreover, the nature of the fat component of low-carbohydrate diets differed considerably between studies, which is a potential confounder of study outcomes, because distinct fatty acids differentially affect (glucose) metabolism (101). In addition, the quality of the carbohydrate component (simple or complex) of interventions often remains obscure, although it is of critical importance for the metabolic response to dietary regimes (102). Numerous other aspects differed considerably between studies, including calorie content, exercise prescription, provision of food by the study center, and reporting of actual food intake. Medication regimes (glucose-, blood pressure–, and lipid-lowering) were modified in some studies, whereas they remained unchanged in others. Some of the studies included medication-naïve patients, whereas other reports failed to document medication details adequately. Notably, and significantly, in all of the studies that included patients taking medication and that adequately reported eventual adaptations (66, 73, 83, 93), with the exception of one (67), glucose-lowering drug doses were reduced in participants who consumed low-carbohydrate food, but not in those consuming 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 variables, dating back to 2006 (for a complete list, see **Supplemental Table 7**). Only one of these specifically compared the effects of a low-carbohydrate diet with those of low-fat diets on components of the metabolic syndrome in the treatment of T2D (103). The low-carbohydrate dietary interventions in the studies included in the review contained <40% from carbohydrate, and the low-fat diets contained <25% from 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 the fasted condition. However, the studies included in the review lasted for a maximum of 12 wk, with the vast majority lasting only 2–6 wk, 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), 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 T2D. Instead, the results suggest that, if it fits the patients' preferences, restriction of carbohydrates 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 with those of low-fat diets in persons with T2D, 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 postmeal glucose responses (104). This is probably also true in persons with T2D. 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 T2D.

Finally, because 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, socioeconomic status, and family circumstances, in addition to personal aspects of physiology, should be taken into account (106, 107).

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