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Dose-dependent effect of carbohydrate restriction for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized controlled trials

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ABSTRACT

Background: Carbohydrate restriction is effective for type 2 diabetes management.

Objectives: We aimed to evaluate the dose-dependent effect of carbohydrate restriction in patients with type 2 diabetes.

Methods: We systematically searched PubMed, Scopus, and Web of Science to May 2021 for randomized controlled trials evaluating the effect of a carbohydrate-restricted diet (≤45% total calories) in patients with type 2 diabetes. The primary outcome was glycated hemoglobin (HbA1c). Secondary outcomes included fasting plasma glucose (FPG); body weight; serum total, LDL, and HDL cholesterol; triglyceride (TG); and systolic blood pressure (SBP). We performed random-effects dose-response meta-analyses to estimate mean differences (MDs) for a 10% decrease in carbohydrate intake.

Results: Fifty trials with 4291 patients were identified. At 6 months, compared with a carbohydrate intake between 55%–65% and through a maximum reduction down to 10%, each 10% reduction in carbohydrate intake reduced HbA1c (MD, −0.20%; 95% CI, −0.27% to −0.13%), FPG (MD, −0.34 mmol/L; 95% CI, −0.56 to −0.12 mmol/L), and body weight (MD, −1.44 kg; 95% CI, −1.82 to −1.06 kg). There were also reductions in total cholesterol, LDL cholesterol, TG, and SBP. Levels of HbA1c, FPG, body weight, TG, and SBP decreased linearly with the decrease in carbohydrate intake from 65% to 10%. A U-shaped effect was seen for total cholesterol and LDL cholesterol, with the greatest reduction at 40%. At 12 months, a linear reduction was seen for HbA1c and TG. A U-shaped effect was seen for body weight, with the greatest reduction at 35%.

Conclusions: Carbohydrate restriction can exert a significant and important reduction on levels of cardiometabolic risk factors in patients with type 2 diabetes. Levels of most cardiometabolic outcomes decreased linearly with the decrease in carbohydrate intake. U-shaped effects were seen for total cholesterol and LDL cholesterol at 6 months and for body weight at 12 months. *Am J Clin Nutr* 2022;116:40–56.

Keywords: adiposity, carbohydrate restriction, ketogenic diet, low-carbohydrate diet, randomized controlled trial, obesity, type 2 diabetes

Introduction

Type 2 diabetes is a main cause of death and disability globally. Currently, about 450 million adults live with diabetes, and that number is estimated to increase to 690 million by the year 2045 (1). Individuals with type 2 diabetes have 2- to 3-fold higher risks of developing cardiovascular disease and premature death (2).

According to the American Diabetes Association position statement, carbohydrate-restricted eating plans may improve hyperglycemia and reduce antihyperglycemic medications in patients with type 2 diabetes (3). There exist several systematic reviews and meta-analyses of intervention studies demonstrating the short-term effectiveness of carbohydrate-restricted diets on glycemic control and levels of cardiometabolic risk factors in patients with type 2 diabetes (4–22).

The authors reported no funding received for this study.

Supplemental Tables 1–22, Supplemental Texts 1–3, and Supplemental Figures 1–46 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: FPG, fasting plasma glucose; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; MCID, minimal clinically important difference; RCT, randomized controlled trial; SBP, systolic blood pressure; TG, triglyceride; % calorie, percentage of daily calorie intake from carbohydrate.

Received October 4, 2021. Accepted for publication March 9, 2022.

First published online May 10, 2022; doi: https://doi.org/10.1093/ajcn/nqac066.

Despite the large body of evidence, the 2 important, unresolved issues regarding the effects of carbohydrate-restricted diets in patients with type 2 diabetes are the optimal degree of carbohydrate restriction and the long-term effects of such diets on cardiovascular and renal diseases. Existing reviews indicate that moderate-carbohydrate diets (≤45% to 26%) (14), low-carbohydrate diets (≤25% to 11%) (8), and very-low-carbohydrate diets (≤10%) (16) are all effective dietary interventions for type 2 diabetes management. However, pairwise comparisons used in traditional meta-analyses, and even advanced network meta-analyses, are profoundly limited in their ability to determine the optimal dose of intervention and, thus, to provide the best evidence needed for decision-making.

Evaluating the potential dose-dependent effects in medical research can be useful for selecting the optimum dose at which to implement the most effective interventions (23, 24). However, to our knowledge, there has been no systematic review and meta-analysis of intervention studies evaluating the dose-dependent effects of carbohydrate restriction in patients with type 2 diabetes.

A dose-response meta-analysis of differences in means is a new statistical approach (25) that has recently been used to evaluate the dose-dependent effects of dietary interventions on continuous outcomes (26). To fill the existing gap, we aimed to undertake a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the dose-dependent effects of carbohydrate restriction on glycemic control and levels of traditional cardiometabolic risk factors in adults with existing type 2 diabetes.

Methods

We followed instructions outlined in the Cochrane Handbook for Systematic Reviews of Interventions (27) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Handbook to conduct our systematic review (28). We registered the protocol for our systematic review at PROSPERO as CRD42021247575 (29).

Systematic search

We systematically searched PubMed, Scopus, and Web of Science from inception until May 2021. In consultation with a librarian, we developed and performed the literature search (SS-B and AJ), and pairs of 2 reviewers (SZ-M and BJ; HS and AM) independently and in duplicate screened titles and abstracts and full-text articles. Differences were resolved by discussion with a third reviewer (AJ). The between-reviewer agreement at the full-text screening stage was assessed and reported as Cohen's kappa coefficient (κ) (30). We also screened the reference lists of all published meta-analyses of RCTs on the effects of low-carbohydrate diets in patients with type 2 diabetes. The complete search strategy used to find articles of original research for inclusion in the present systematic review is provided in **Supplemental Table 1**.

Selection criteria

Original, controlled trials with the following criteria were considered eligible for inclusion: *1*) randomized trials with either a parallel or crossover design conducted in adults (≥18 years) with type 2 diabetes, with or without cardiovascular conditions and regardless of medication use or glucose concentration and glycated hemoglobin (HbA1c) level; *2*) trials with an intervention period of 4 weeks or longer; *3*) trials evaluating the effects of a diet with ≤45% carbohydrate (31, 32), with or without a calorie restriction, physical activity, and behavioral support, against a control diet; *3*) trials that considered a change in cardiometabolic risk factors as the outcome of interest; *4*) publications that provided means and SDs of changes in outcomes of interest, or reported sufficient information to estimate those values; and *5*) trials that provided amounts of dietary carbohydrate intake (percentage energy or grams per day) in both the intervention and control groups.

Eligible control groups included waitlist controls, dietary advice, or any active controls, including those competing for dietary programs higher in carbohydrate (>45%), with or without exercise or lifestyle and behavioral recommendations.

Outcomes

For the present review, we considered a change in HbA1c as the primary outcome. Secondary outcomes included changes in body weight, fasting plasma glucose (FPG), LDL cholesterol, HDL cholesterol, total cholesterol, triglyceride (TG), and systolic blood pressure (SBP). All outcomes were assessed separately across 3 time periods, including 1 to ≤6 months (6-month follow-up), 6 to ≤12 months (12-month follow-up), and >12 months.

Exclusion criteria

We excluded trials *1*) with an intervention period shorter than 4 weeks; *2*) conducted in patients with a history of cancer, pregnant women, children, and adolescents; and *3*) that did not report sufficient information to estimate the percentages of daily calorie intake from carbohydrate (% calorie). To be included in this review, trials must report % calorie data from carbohydrates—or report the amount of carbohydrate intake in the form of grams per day, as well as the daily calorie intake, to calculate the % calorie values from carbohydrates—in both the intervention and control groups. Trials without this information either in the intervention or in the control group were excluded.

Data extraction

After the study selection process, a pair of 2 reviewers (AJ and SZ-M) independently and in duplicate extracted the following characteristics from each trial: the last name of the first author; year of publication; study design (parallel or crossover); sample size; mean age; baseline weight status; intervention duration; description of intervention and control arms; the percentages of calories obtained from carbohydrate, fat, and protein in both the intervention and control groups; calorie restriction (yes or no; if yes, kcal restriction details); exercise and/or physical activity; behavioral support (yes or no; if yes, behavioral support details); and means and corresponding SDs of changes in outcomes from baseline for each arm. Disagreements were resolved by consensus between the 2 authors. For trials reporting different effect sizes across 1 time period (e.g., 3 and 6 months), the results for the longest duration in each period were included.

Risk of bias assessment

Two authors (AJ and SS-B) independently assessed the risk of bias of the trials using guidance outlined in the Cochrane tool for

risk of bias tool (26). Disagreements were resolved by consensus. For outcomes that included trials with both high and low risks of biases, we performed a prespecified subgroup analysis based on the study quality (low risk compared with high risk or some concerns). When there was no significant subgroup difference, we included all trials in the main analysis. When trials with a low risk of bias showed different results and the *P* value for a subgroup difference was significant, we reported the results in the subgroup of trials with a low risk of bias (33).

Data analyses

We performed separate dose-response meta-analyses for each outcome in each time period (1 to ≤6 months, 6 to ≤12 months, and >12 months) using the DerSimonian and Laird random-effects meta-analyses (34). We selected mean differences and 95% CIs of changes in primary and secondary outcomes in the intervention group relative to the control group as the effect size for reporting the results of the present systematic review.

First, we calculated changes from baseline values in each study arm. If the mean values and SDs of changes were not available in text or graphs, we calculated these values using data from measures before and after the intervention, based on the Cochrane Handbook guidance (26). For trials that reported SEs instead of SDs, the former were converted to SDs (26). If neither SDs nor SEs were reported in the trials, we used the average SDs obtained from other trials included in the meta-analysis (35). For trials that reported median data instead of mean data, we converted the former to mean data using standard methods (36, 37).

Second, we used the method introduced by Crippa and Orsini (25) to calculate the mean differences and their corresponding SEs of changes in outcomes for each 10% decrease in calorie intake from carbohydrate, compared with a carbohydrate intake between 55%–65% and through a maximum reduction down to 10%, in the intervention group relative to the control group in each trial. Trial-specific results were pooled using a random-effects model (34). This method requires the dose of carbohydrate intake (% calorie) in each study arm, the mean and its corresponding SD of change in each study arm, and the number of participants in each arm. For trials that reported carbohydrate intake in the form of grams per day, we converted it to % calorie using the average calorie intake reported in those trials. For trials that reported carbohydrate intake as a range (e.g., 50% to 60%), the midpoint of the lower and upper bounds was used. When trials presented both prescribed and actual (self-reported) dietary data, we used self-reported data for the analyses. For trials without information on self-reported dietary intake, prescribed data were used. For trials that presented self-reported dietary data across different time periods, we used period-specific, self-reported dietary data. For example, when trials reported self-reported percentages of carbohydrate intake at the 6-month and 12-month follow-ups, we included period-specific data for the corresponding meta-analyses. For trials that reported percentages of carbohydrate intake at different intervals in 1 time period (e.g., reported percentages of carbohydrate intakes at the 3-month and 6-month follow-ups), we used the average carbohydrate intake over each time period for the analyses.

Based on our a priori protocol (29), we performed prespecified subgroup analyses based on the baseline weight (overweight or obese compared with normal weight); risk of bias (low risk compared with high risk or some concerns); presence of calorie restrictions, physical activity, or behavioral support in the intervention program; and percentage of protein (% calorie) in the intervention group (≤20%, 20% to 24.9%, and ≥25%). Diets with ≤20%, 20% to 24.9%, and ≥25% of calories from protein were considered to have low, moderate, and high protein, respectively (38). We calculated *P* values for subgroup difference using a meta-regression analysis. We considered subgroup differences credible based on 8 criteria introduced by the Instrument to Assess the Credibility of Effect Modification Analyses (ICEMAN) (39). We also performed post hoc subgroup analyses based on insulin use, baseline glycemic control status, type of control diet (low-fat compared with healthy or dietary advice diet), calorie matching, and method of dietary assessment (self-reported compared with prescribed). Stratified analyses based on self-reported dietary data rather than prescribed dietary data are included in the unresolved issues that need to be investigated in the context of low-carbohydrate diets (40).

We performed an influence analysis to test the potential impact of each trial on the main results. Publication bias was tested using Egger's test ($P < 0.05$) (41) and inspection of the funnel plot when ≥10 trials were available for the analysis. We evaluated heterogeneity using the I^2 statistic (>50% as substantial heterogeneity) and performed a χ^2 test for homogeneity ($P_{heterogeneity} > 0.10$) (26). Finally, we performed a dose-response meta-analysis to illustrate the dose-dependent effect of carbohydrate restriction on primary and secondary outcomes. Nonlinear dose-response associations were assessed with restricted cubic splines with 3 knots at Harrell's recommended centiles (10%, 50%, and 90%) (42). To present a comprehensive and comparable picture of the effects of low-carbohydrate diets for type 2 diabetes management, we translated the effect sizes in the intervention and control groups to percentage changes from baseline values in those groups, and then repeated the nonlinear dose-response meta-analyses using percentage change data to show all effects in 1 figure. Detailed descriptions about the method used for the nonlinear dose-response meta-analyses and STATA syntax used for the analyses are provided in **Supplemental Texts 1** and **2**, respectively. Statistical analyses were conducted using STATA software version 16.0. A 2-tailed *P* value less than 0.05 was considered significant.

Grading the evidence

We applied the GRADE approach to rate the overall certainty of the evidence for each outcome in each time period (43). A pair of authors (AJ and SS-B) independently performed GRADE assessments. The between-reviewer agreement was assessed and reported as Cohen's kappa coefficient (κ) (30). A GRADE assessment rates the certainty of evidence as high, moderate, low, or very low. In brief, the criteria used to downgrade evidence include risk of bias, inconsistency, indirectness, imprecision, and publication bias. To rate for imprecision, we used recently reported minimal clinically important difference (MCID) thresholds for cardiovascular risk factors in patients with type 2 diabetes, including HbA1c (0.50%), body weight (4.4 kg), total cholesterol (0.26 mmol/L), LDL cholesterol (0.10 mmol/L), HDL cholesterol (0.10 mmol/L), TG (0.09 mmol/L), SBP (2 mmHg), and FPG (1.60 mmol/L) (8). The criteria to upgrade evidence include a large effect size and dose-response gradient. Because

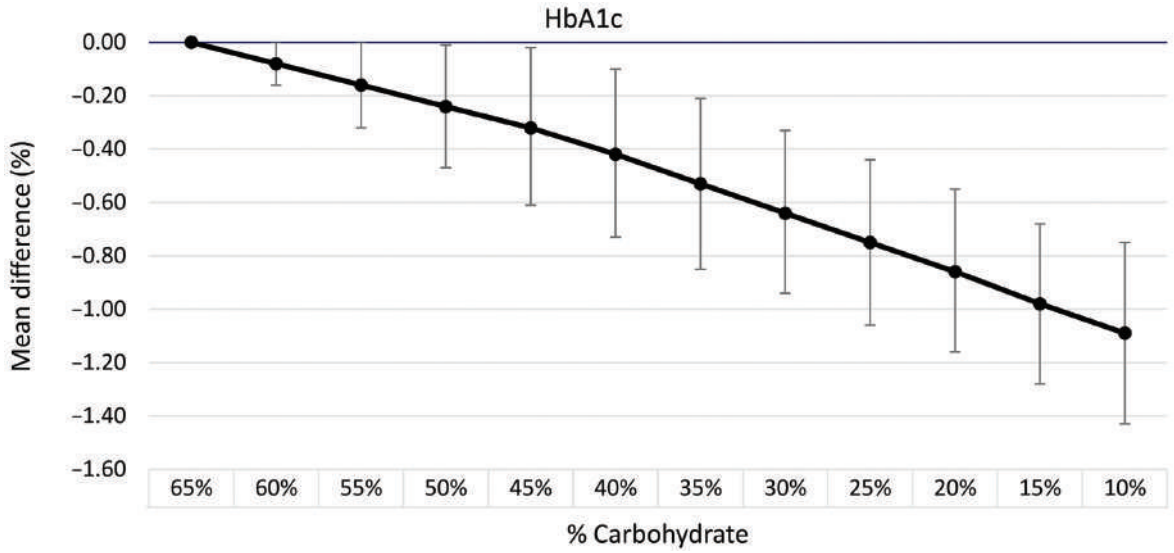

FIGURE 1 Dose-dependent effect of carbohydrate restriction on HbA1c (%) in patients with type 2 diabetes at the 6-month follow-up ($n = 29$ trials). HbA1c, glycated hemoglobin.

we performed dose-response meta-analyses, we were able to upgrade evidence when there were significant dose-dependent effects in the analyses. Detailed information about the domains of the GRADE tool and how to judge each domain are provided in **Supplemental Text 3**.

Results

Literature search and study selection process

As described in **Supplemental Figure 1**, the initial database and reference list searches identified 7885 records. After excluding 1992 duplicates and 5655 irrelevant articles based on screening of the title and abstract, 238 full-texts were reviewed in detail for eligibility. Overall, 50 articles provided sufficient information and were considered eligible to be included in this dose-response meta-analysis. The between-reviewer agreement for including studies was near perfect (Cohen's kappa = 0.87) at the full-text screening step. The list of studies excluded via full-text assessment, with reasons for exclusions, is provided in **Supplemental Table 2**.

Characteristics of primary trials included in the dose-response meta-analysis

Supplemental Table 3 summarizes the general characteristics of 50 primary trials, with 4291 patients with type 2 diabetes, included in this dose-response meta-analysis (44–93). In brief, included trials were published between 1981 and 2021. All trials included adults with type 2 diabetes and were conducted in the outpatient setting. The median intervention duration was 24 weeks (range, 5–208 weeks), with 3 trials shorter than 12 weeks (44, 56, 78). The median sample size was 63 participants (range, 10–419 participants). Of the trials, 35 were conducted exclusively in adults with overweight and obesity (BMI $\geq$ 25 kg/m^2) (44–47, 49, 50, 52–55, 57, 58, 61, 63, 64, 66, 67, 70–75, 77, 79–85, 88, 89, 91, 93), and the other 15 trials in mixed-weight populations (48, 51, 56, 59, 60, 62, 65, 68, 69, 76, 78, 86, 87, 90, 92). Nineteen trials excluded patients with type 2 diabetes who used insulin treatment (44, 45, 47, 51–54, 57, 62, 63, 65, 68, 72, 79, 84, 86, 90, 91, 93), 1 trial included patients with insulin-dependent type 2 diabetes (56), and the other 30 trials included a mix of patient insulin regimes (46, 48–50, 55, 58–61, 64, 66, 67, 69–71, 73–78, 80–83, 85, 87–89, 92). Twelve trials were conducted in those with good glycemic control (44, 45, 54, 56, 57, 62, 63, 68, 79, 80, 84, 86), 4 in those with poor control (48, 49, 81, 92), and 34 included populations with different levels of glycemic control (46, 47, 50–53, 55, 58–61, 64–67, 69–78, 82, 83, 85, 87–91, 93).

Of the included trials, 39 implemented behavioral support in parallel with a low-carbohydrate diet (44–47, 49, 50, 53–55, 57–64, 66–70, 72–77, 79–83, 85, 88–91, 93), 34 implemented calorie restriction (45–52, 54, 55, 57, 59, 63, 64, 66, 67, 69, 71–75, 77–81, 83–85, 88, 89, 91, 92), and 14 implemented supervised or structured exercise programs (44, 54, 58, 61, 62, 67, 74, 76, 80, 83, 88, 89, 91, 93). Forty trials had a conventional low-fat diet as a control diet (44–48, 50, 54–57, 59, 60, 62–64, 66–76, 78, 81–93), and the other 10 trials had a healthy diet or dietary advice as the control arm (48, 51–53, 58, 61, 65, 77, 79, 80). The median percentages of calories from carbohydrates in the intervention and control arms were 35% (range, 10%–45%) and 52% (range, 45%–65%), respectively. The median difference in percentages of calories from carbohydrate between intervention and control arms was 15% (range, 3%–40%), and the average difference was 17.5% $\pm$ 8.8%. The median percentages of calories from protein and fat in the intervention arms were 25% (range, 10%–50%) and 40% (range, 15%–60%), respectively. One trial implemented a very-low-carbohydrate diet ($\leq$10%) as the intervention, 10 trials implemented a low-carbohydrate diet (11% to 26%), and the other 39 trials implemented a moderate-carbohydrate diet (26% to 45%). Of the included trials, 25 assessed dietary intake and presented self-reported dietary data during the intervention period (44–46, 49–53, 59–63, 66, 67, 69, 77, 79–81, 83, 85–88), and the other 25 reported prescribed dietary information (47, 48, 54–58, 64, 65, 68, 70–76, 78, 82, 84, 89–93). In 6

TABLE 1 Summary of the effect of carbohydrate restriction (10% decrease) on cardiometabolic outcomes in patients with type 2 diabetes[1]

Outcome	1 to 6 months			6 to 12 months			≥12 months		
	Participants (trials)	Mean difference (95% CI)	GRADE	Participants (trials)	Mean difference (95% CI)	GRADE	Participants (trials)	Mean difference (95% CI)	GRADE
HbA1c, %	2461 (29)	−0.20 (−0.27 to −0.13)	High	1222 (13)	−0.11 (−0.18 to −0.05)	High	256 (3)	−0.20 (−0.37 to −0.03)	Low
FPG, mmol/L	2145 (25)	−0.34 (−0.56 to −0.12)	High	1093 (9)	−0.32 (−0.74 to 0.10)	Low	123 (2)	−0.10 (−0.70 to 0.51)	Very low
Weight, kg	2773 (35)	−1.44 (−1.82 to −1.06)	High	1838 (17)	−1.34 (−1.78 to −0.91)	Moderate	254 (3)	−0.09 (−0.96 to 0.77)	Low
TC, mmol/L	2252 (24)	−0.06 (−0.15 to 0.02)	Moderate	1179 (10)	0.00 (−0.16 to 0.16)	Low	256 (3)	−0.08 (−0.25 to 0.08)	Low
LDL-C, mmol/L	2421 (26)	−0.08 (−0.13 to −0.03)	High	352 (3)[2]	−0.13 (−0.23 to −0.02)	Low	256 (3)	−0.15 (−0.32 to 0.02)	Low
HDL-C, mmol/L	2574 (25)	0.02 (0.00–0.03)	Low	1406 (13)	−0.03 (−0.07 to 0.01)	Very low	123 (2)	−0.01 (−0.14 to 0.12)	Low
TG, mmol/L	2717 (30)	−0.12 (−0.18 to −0.06)	High	1423 (13)	−0.12 (−0.23 to −0.02)	High	123 (2)	−0.19 (−0.47 to 0.08)	Low
SBP, mmHg	1997 (21)	−1.79 (−2.96 to −0.61)	High	298 (3)[2]	−1.24 (−2.54 to 2.56)	Moderate	123 (2)	0.67 (−2.60 to 3.93)	Low

[1]The results are from a random-effects meta-analysis. FPG, fasting plasma glucose; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.
[2]We found statistically significant differences between studies at high risk of bias and those at low risk of bias. Here, we reported results from studies at low risk of bias.

trials, carbohydrate intake was reported as a range either in the intervention or in the control arm; therefore, we used the midpoint of the range as the percentage of carbohydrate intake for the analyses (53, 57, 59, 60, 79, 92). In 9 trials, carbohydrate intake was reported in the form of grams per day; thus, we converted the data to % calorie using the average calorie intakes reported in those trials (48, 49, 57, 58, 70, 80, 81, 87, 89). Twenty trials (40%) were rated to have a low risk of bias (44, 45, 48, 50, 54–56, 62, 63, 70, 76, 78–84, 87, 93), 9 (18%) were rated to have some concerns (52, 53, 60, 67–69, 74, 85, 90), and 21 (42%) were rated to have a high risk of bias (46, 47, 49, 51, 57–59, 61, 64–66, 71–73, 75, 77, 86, 88, 89, 91, 92) (**Supplemental Table 4**).

Primary outcome

At the 6-month follow-up, each 10% reduction in carbohydrate intake, compared with a carbohydrate intake between 55%–65% and through a maximum reduction down to 10%, reduced HbA1c by 0.20% (95% CI, −0.27% to −0.13%; $n = 29$ trials with 2461 participants; GRADE = high certainty; **Supplemental Figure 2**) (44–47, 49, 50, 61–69, 72, 73, 75–81, 84, 86–89). The dose-response meta-analysis indicated a linear reduction, wherein levels of HbA1c reduced linearly from 65% to 10% carbohydrate (**Figure 1**). At the 12-month follow-up, each 10% decrease in carbohydrate intake reduced HbA1c (mean difference, −0.11%; 95% CI, −0.18% to −0.05%; $n = 13$ trials with 1222 participants; GRADE = high certainty; **Supplemental Figure 3**) (45, 50, 60, 61, 66, 67, 74, 75, 80, 85, 90–92). The dose-response meta-analysis indicated a linear reduction in HbA1c (**Supplemental Figure 4**). At follow-ups longer than 12 months, each 10% decrease in carbohydrate intake lead to a 0.20% reduction in HbA1c (95% CI, −0.37% to −0.03%; $n = 3$ trials with 256 participants; GRADE = low certainty; **Supplemental Figure 5**) (46, 48, 60).

Secondary outcomes

The effects of carbohydrate restriction on secondary outcomes across 3 time periods are presented in **Table 1** and **Supplemental Figures 6–30**. At the 6-month follow-up, each 10% decrease in carbohydrate reduced FPG by 0.34 mmol/L (95% CI, −0.56 to −0.12 mmol/L; $n = 25$ trials with 2145 participants; GRADE = moderate certainty; Supplemental Figure 6) (44–47, 61–63, 66, 68, 69, 71–73, 75–79, 83, 84, 86–89, 93). There was a monotonic reduction in FPG with the decrease in carbohydrate intake (**Figure 2**). Carbohydrate restriction did not lead to a significant reduction in FPG at the 12-month follow-up (Supplemental Figures 7–8) (45, 61, 66, 74, 75, 83, 85, 91, 92), nor at follow-ups longer than 12 months (Supplemental Figure 9) (46, 48).

At the 6-month follow-up, a 10% decrease in carbohydrate intake reduced body weight (mean difference, –1.44 kg; 95% CI, –1.82 to –1.06 kg; $n = 35$ trials with 2773 participants; GRADE = high certainty; Supplemental Figure 10) (44–47, 49–52, 55–59, 61–69, 71–73, 76, 78–80, 83, 84, 86, 88, 89, 93). There was a sharp linear reduction in body weight with the decrease in carbohydrate intake (**Figure 3**). At the 12-month follow-up, each 10% decrease in carbohydrate intake reduced body weight by 1.34 kg (95% CI, −1.78 to −0.91 kg; $n = 17$ trials with

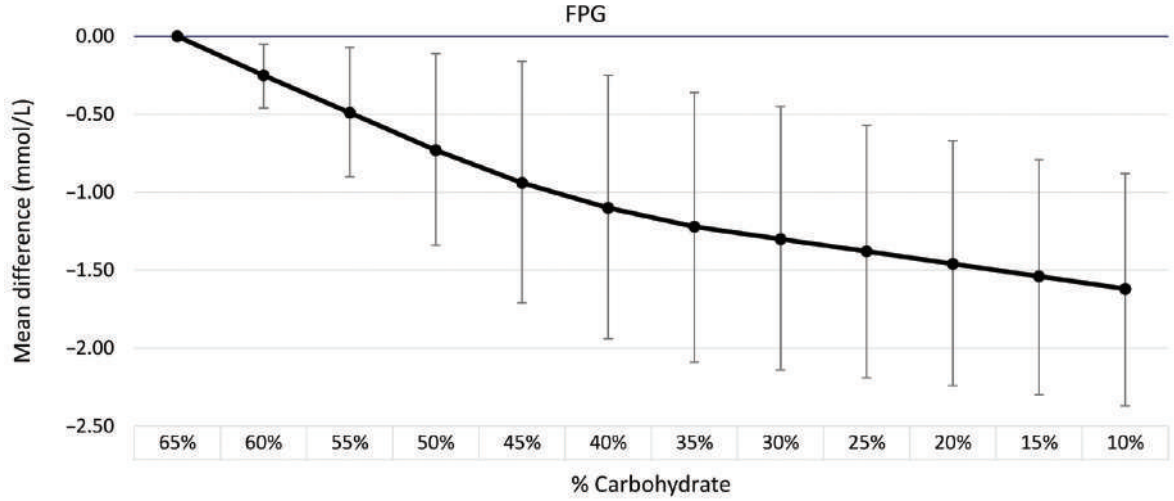

FIGURE 2 Dose-dependent effect of carbohydrate restriction on FPG (mmol/L) in patients with type 2 diabetes at the 6-month follow-up ($n = 25$ trials). FPG, fasting plasma glucose.

1838 participants; GRADE = moderate certainty; Supplemental Figure 11) (45, 46, 50, 53, 54, 58, 59, 61, 66, 67, 74, 80, 83, 85, 90–92). There was a U-shaped effect in the dose-response meta-analysis (**Figure 4**), with the greatest reduction at 35% carbohydrate (mean difference$_{35\%}$, −3.57 kg; 95% CI, −6.32 to −0.82) kg. There was not significant reduction in body weight at follow-ups longer than 12 months (Supplemental Figure 12) (46, 48, 54).

At the 6-month follow-up, each 10% decrease in carbohydrate intake reduced LDL cholesterol (mean difference, −0.08 mmol/L; 95% CI, −0.13 to −0.03 mmol/L; $n = 26$ trials with 2421 participants) (44–46, 50, 61–63, 66–69, 71, 73, 75–81, 83, 84, 86, 88, 89, 93), TG (mean difference, −0.12 mmol/L; 95% CI, −0.18 to −0.06 mmol/L; $n = 30$ trials with 2717 participants) (44–47, 49–51, 61–63, 66–69, 71–73, 75–81, 83, 84, 86, 88, 89, 93), and SBP (mean difference, −1.79 mmHg; 95% CI, −2.96 to −0.61 mmHg; $n = 21$ trials with 1997 participants) (45, 46, 49, 50, 61–63, 66–69, 71, 72, 78, 79, 82–84, 86, 88, 89), with the certainty of evidence being rated high. Carbohydrate restriction led to a nonsignificant reduction in total cholesterol (44–46, 50, 51, 61–63, 66–68, 71–73, 75–78, 84, 86–89, 93) and a nonsignificant increase in HDL cholesterol (**Figure 5**) (44–47, 61–63, 66–69, 71–73, 75–79, 83, 84, 86, 88, 89, 93).

The dose-response meta-analysis indicated U-shaped effects for total cholesterol and LDL cholesterol, with the greatest reduction at 40% [total cholesterol: mean difference$_{40\%}$, −0.39 mmol/L (95% CI, −0.63 to −0.15 mmol/L; **Figure 6**); LDL cholesterol: mean difference$_{40\%}$, −0.35 mmol/L (95% CI, −0.55 to −0.15 mmol/L; **Figure 7**)]. Levels of TG and SBP decreased linearly with the decrease in carbohydrate intake (**Figures 8 and 9**). Point-specific effects of carbohydrate restriction on cardiometabolic outcomes at the 6-month

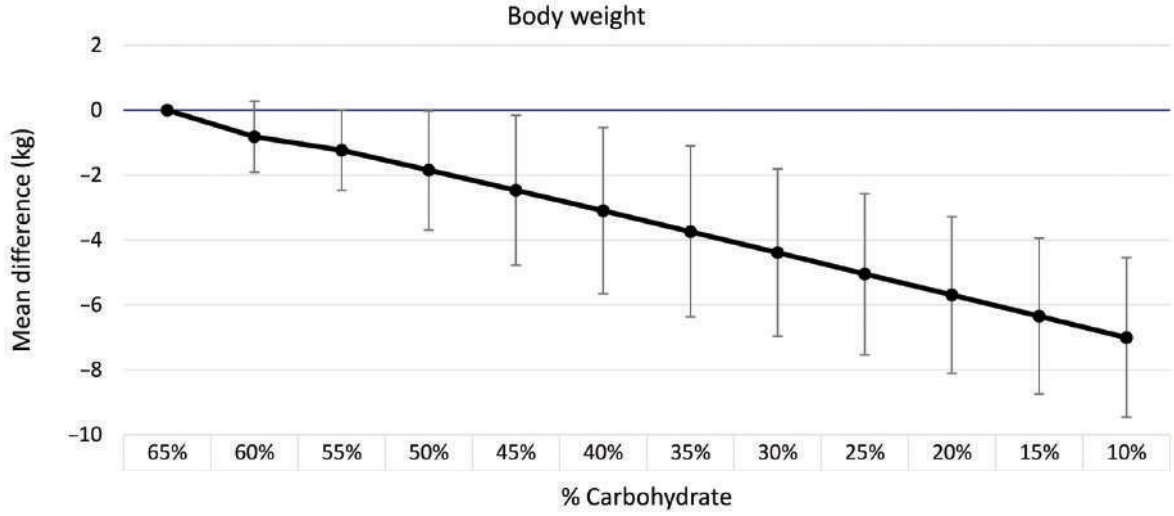

FIGURE 3 Dose-dependent effect of carbohydrate restriction on body weight (kg) in patients with type 2 diabetes at the 6-month follow-up ($n = 35$ trials).

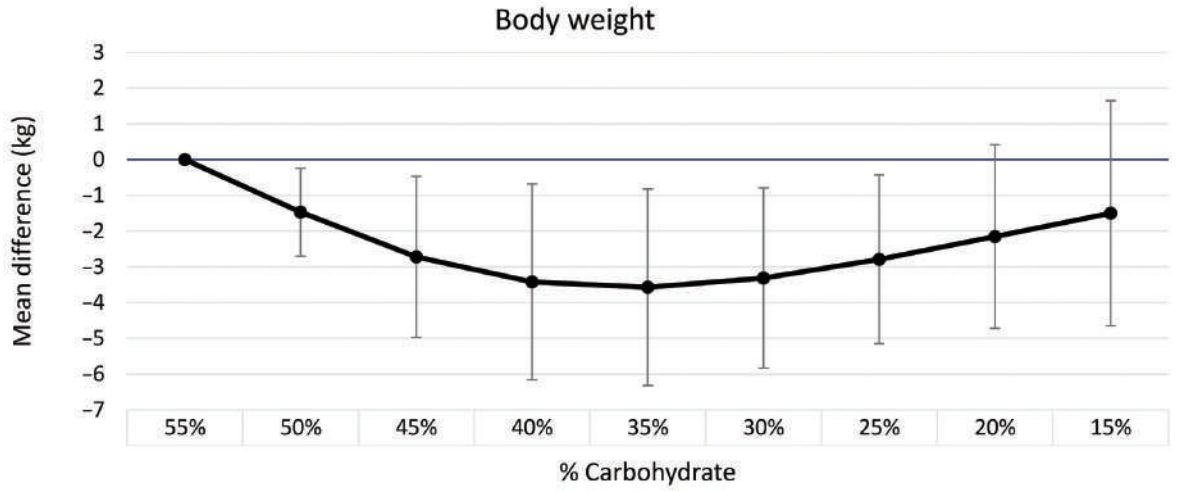

FIGURE 4 Dose-dependent effect of carbohydrate restriction on body weight (kg) in patients with type 2 diabetes at the 12-month follow-up ($n = 17$ trials).

follow-up are summarized in **Table 2** and **Supplemental Figure 31**.

At the 12-month follow-up, a 10% decrease in carbohydrate intake resulted in significant reductions in TG (mean difference, −0.12 mmol/L; 95% CI, −0.23 to −0.02 mmol/L; $n = 13$ trials with 1423 participants; GRADE = high certainty) (45, 50, 61, 66, 67, 74, 75, 80, 83, 85, 90–92) and LDL cholesterol (mean difference, −0.13 mmol/L; 95% CI, −0.23 to −0.02 mmol/L; $n = 3$ trials with 352 participants and low risk of bias; GRADE = low certainty) (45, 80, 83). Serum TG decreased linearly with the decrease in carbohydrate intake from 55% to 15% (**Figure 10**). Point-specific effects of carbohydrate restriction on cardiometabolic outcomes at the 12-month follow-up are presented in **Supplemental Table 5**. We did not find significant reductions in secondary outcomes at follow-ups longer than 12 months (Table 1).

Sensitivity and subgroup analyses

In prespecified influence analyses, the main results remained stable and did not change materially after the exclusion of any single trial from the analyses, indicating that the main findings have not been affected largely by a single trial. Sequential exclusion of each trial did not change the significance of the effect sizes across time periods. Sensitivity analyses did not explain the observed heterogeneity in the data; the exception was SBP at the 6-month follow-up, where the exclusion of 1 trial (90) explained part of the heterogeneity (mean difference, −1.53; 95% CI, −2.65 to −0.24; $I^2 = 44\%$).

Based on our a priori protocol, we did subgroup analyses to test for potential effect modifications by calorie restriction, physical activity, behavioral support, baseline weight status, risk of bias, and percentage of protein intake in the intervention arm at the 6-month and 12-month follow-ups (**Supplemental Tables 6–21**).

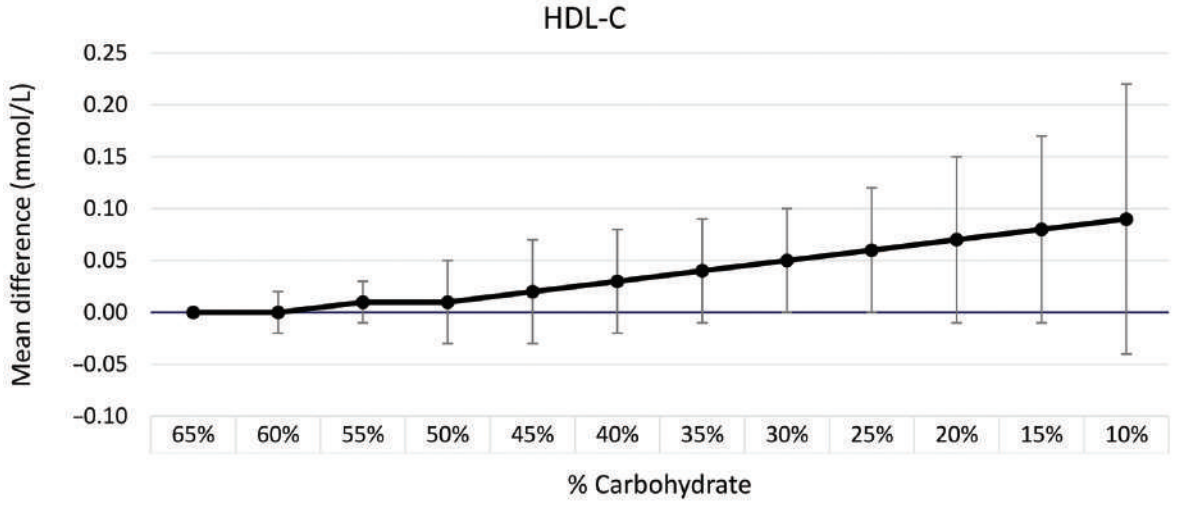

FIGURE 5 Dose-dependent effect of carbohydrate restriction on HDL cholesterol (mmol/L) in patients with type 2 diabetes at the 6-month follow-up ($n = 25$ trials).

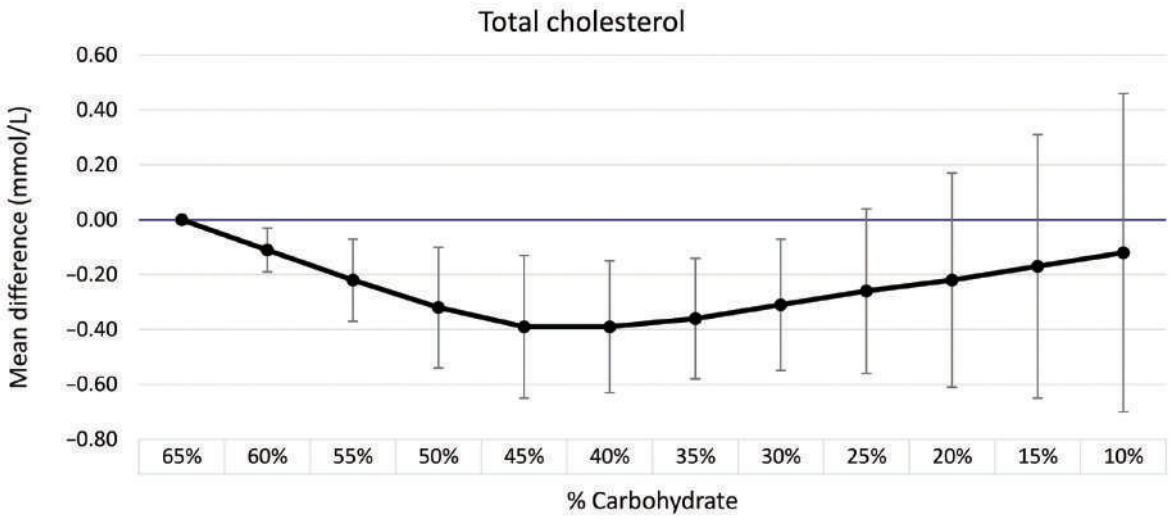

FIGURE 6 Dose-dependent effect of carbohydrate restriction on total cholesterol (mmol/L) in patients with type 2 diabetes at the 6-month follow-up ($n = 24$ trials).

Based on 8 criteria to identify credible subgroup differences (39), we identified 4 credible subgroup differences at the 6-month follow-up. In the subgroup based on the percentage of protein intake in the intervention arm, studies with 20% to 25% protein intake indicated larger reductions in FPG (mean difference, −0.67 mmol/L; 95% CI, −0.99 to −0.35 mmol/L; $n = 9$ trials) than trials with ≤20% protein (mean difference, 0.02 mmol/L; 95% CI, −0.32 to 0.28 mmol/L; $n = 6$ trials) and ≥25% protein (mean difference, −0.23 mmol/L; 95% CI, −0.57 to 0.11 mmol/L; $n = 10$ trials; test for subgroup difference = 0.02); also, studies with ≥25% protein indicated greater reductions in body weight (mean difference, −1.86 kg; 95% CI, −2.68 to −1.03 kg; $n = 20$ trials) than those with ≤20% protein (mean difference, −0.32 kg; 95% CI, −1.43 to 0.78 kg; $n = 6$ trials) and 20% to 25% protein (mean difference, −1.19 kg; 95% CI, −1.71 to −0.07 kg; $n = 9$ trials; test for subgroup difference = 0.02). For total cholesterol, studies that included patients with good glycemic control indicated significant reductions (mean difference, −0.13 mmol/L; 95% CI, −0.22 to −0.04 mmol/L; $n = 8$ trials), while studies that included populations with mixed levels of glycemic control indicated nonsignificant reductions (mean difference, −0.03 mmol/L; 95% CI, −0.14 to 0.08 mmol/L; $n = 16$ trials; test for subgroup difference = 0.04). Studies that implemented calorie restriction also showed greater reductions in TG (mean difference, −0.14 mmol/L; 95% CI, −0.19 to −0.09 mmol/L; $n = 23$ trials) than trials that did not (mean difference, −0.06 mmol/L; 95% CI, −0.23 to 0.10 mmol/L; $n = 7$ trials; test for subgroup difference = 0.01).

We also performed a post hoc subgroup analysis based on the method of dietary data presentation. A greater reduction in total cholesterol was seen in studies that reported prescribed dietary data (mean difference, −0.07 mmol/L; 95% CI, −0.12 to −0.01

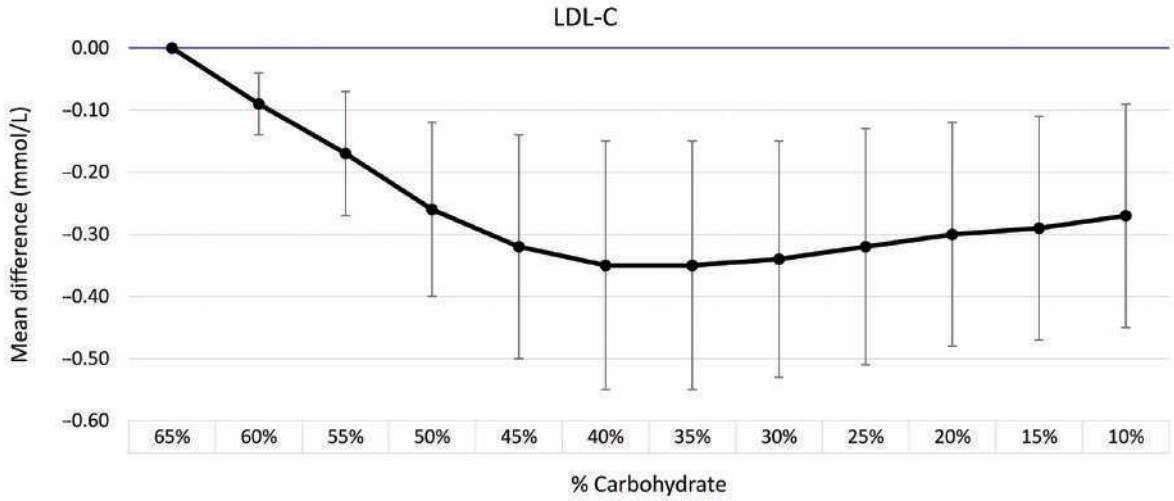

FIGURE 7 Dose-dependent effect of carbohydrate restriction on LDL cholesterol (mmol/L) in patients with type 2 diabetes at the 6-month follow-up ($n = 26$ trials).

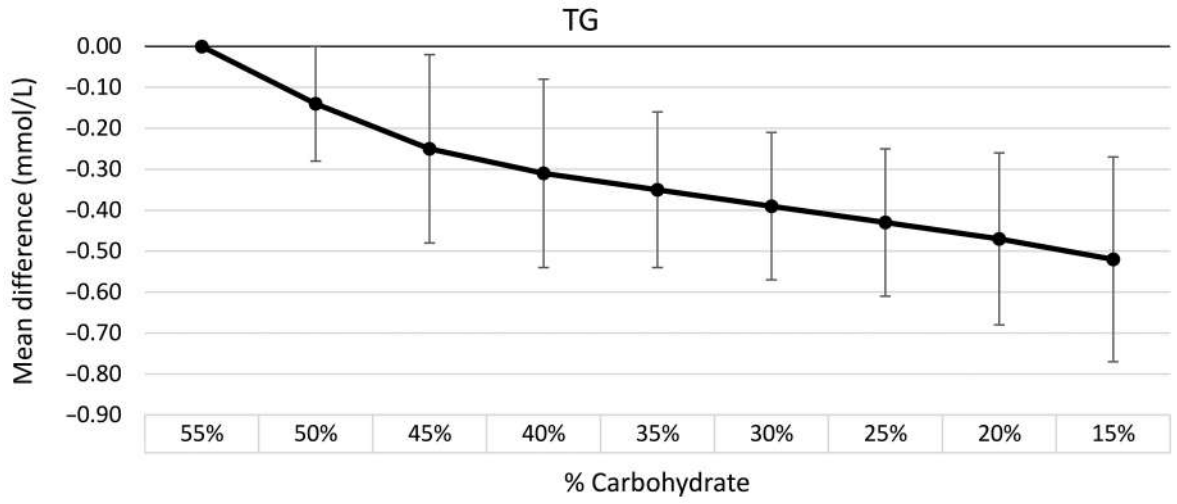

FIGURE 8 Dose-dependent effect of carbohydrate restriction on TG (mmol/L) in patients with type 2 diabetes at the 6-month follow-up ($n = 30$ trials). TG, triglyceride.

mmol/L; $n = 12$ trials) than in studies that presented self-reported dietary data (mean difference, 0.00 mmol/L; 95% CI, −0.16 to 0.17 mmol/L; $n = 14$ trials; test for subgroup difference = 0.01). However, the observed subgroup difference may be due to the chance, as the analysis of TG indicated an opposite finding, where studies with self-reported dietary data indicated significantly greater reductions (mean difference, −0.15 mmol/L; 95% CI, −0.19 to −0.10 mmol/L; $n = 17$ trials) than studies reporting prescribed dietary data (mean difference, −0.09 mmol/L; 95% CI, −0.20 to 0.02 mmol/L; $n = 13$ trials; test for subgroup difference = 0.01).

At the 12-month follow-up, there was a potential effect modification by physical activity for HDL cholesterol, where studies implementing exercise indicated a null effect (mean difference, 0.00 mmol/L; 95% CI, −0.08 to 0.07 mmol/L; $n = 7$ trials), whilst studies without exercise indicated a reduction in HDL cholesterol (mean difference, −0.06 mmol/L; 95% CI, −0.08 to −0.04 mmol/L; $n = 6$ trials; test for subgroup difference = 0.001). There was also evidence of effect modifications by behavioral support for TG (test for subgroup difference < 0.001) and by calorie restriction for body weight (test for subgroup difference = 0.03), where studies implementing behavioral support and calorie restriction indicated greater reductions.

There was also a significant subgroup difference for risk of bias in the analyses of LDL cholesterol and SBP at the 12-month follow-up, where there was a statistical difference between studies at high risk of bias and those at low risk of bias. Therefore,

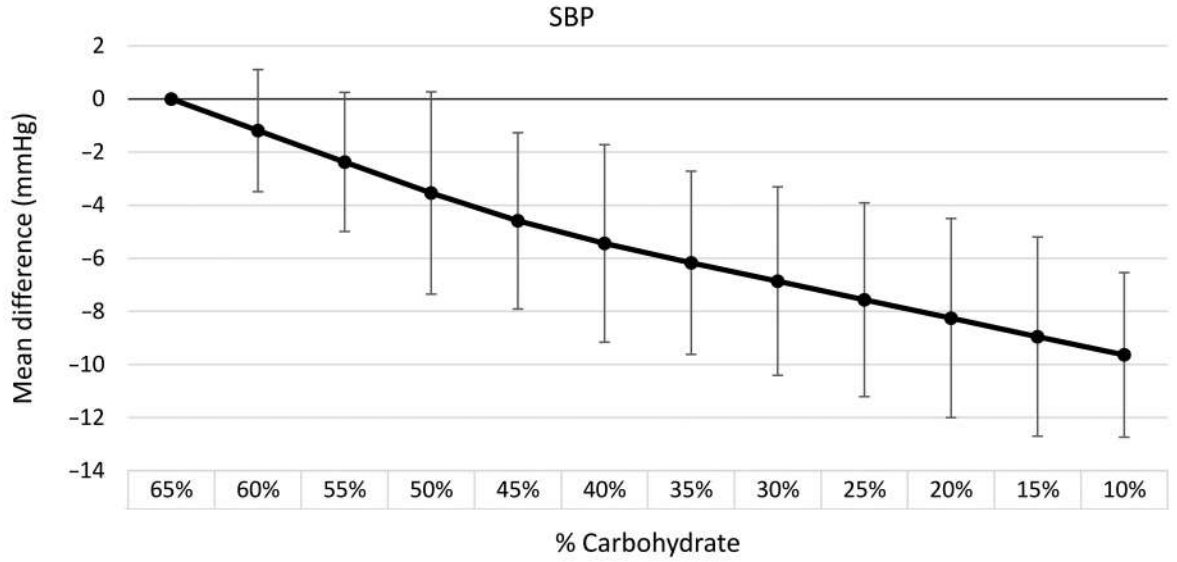

FIGURE 9 Dose-dependent effect of carbohydrate restriction on SBP (mmHg) in patients with type 2 diabetes at the 6-month follow-up ($n = 21$ trials). SBP, systolic blood pressure.

TABLE 2 The effects of carbohydrate restriction on cardiometabolic outcomes at the 6-month follow-up form the nonlinear, dose-response meta-analysis (mean difference and 95% CI)[1]

Carbohydrate intake, % calorie	65% (Ref)	55%	45%	40%	35%	30%	25	20%	15%	10%
FPG, mmol/L	0	−0.25 (−0.45 to −0.04)	−0.94 (−1.72 to −0.17)	−1.10 (−1.95 to −0.25)	−1.22 (−2.08 to −0.35)	−1.30 (−2.15 to −0.46)	−1.38 (−2.19 to −0.57)	−1.46 (−2.25 to −0.68)	−1.54 (−2.30 to −0.78)	−1.62 (−2.36 to −0.88)
HbA1c, %	0	−0.16 (−0.32 to 0.00)	−0.32 (−0.62 to −0.03)	−0.42 (−0.74 to −0.10)	−0.53 (−0.85 to −0.20)	−0.64 (−0.95 to −0.32)	−0.75 (−1.06 to −0.44)	−0.86 (−1.17 to −0.56)	−0.98 (−1.29 to −0.67)	−1.09 (−1.42 to −0.77)
Weight, kg	0	−1.23 (−2.47 to 0.01)	−2.47 (−4.78 to −0.16)	−3.10 (−5.67 to −0.54)	−3.74 (−6.38 to −1.11)	−4.39 (−6.97 to −1.81)	−5.05 (−7.53 to −2.56)	−5.70 (−8.12 to −3.28)	−6.35 (−8.76 to −3.94)	−7.01 (−9.47 to −4.54)
TC, mmol/L	0	−0.22 (−0.38 to −0.07)	−0.39 (−0.65 to −0.13	−0.39 (−0.63 to −0.15)	−0.36 (−0.57 to −0.14)	−0.31 (−0.55 to −0.07)	−0.26 (−0.56 to 0.04)	−0.22 (−0.60 to 0.17)	−0.17 (−0.65 to 0.31)	−0.12 (−0.71 to 0.46)
LDL-C, mmol/L	0	−0.17 (−0.27 to −0.07)	−0.32 (−0.50 to −0.14)	−0.35 (−0.55 to −0.15)	−0.35 (−0.55 to −0.15)	−0.34 (−0.53 to −0.14)	−0.32 (−0.51 to −0.13)	−0.30 (−0.49 to −0.12)	−0.29 (−0.47 to −0.11)	−0.27 (−0.45 to −0.09)
HDL-C, mmol/L	0	0.01 (−0.02 to 0.03)	0.02 (−0.03 to 0.06)	0.03 (−0.02 to 0.07)	0.04 (−0.01 to 0.08)	0.05 (−0.01 to 0.10)	0.06 (−0.01 to 0.12)	0.07 (−0.02 to 0.15)	0.08 (−0.03 to 0.19)	0.09 (−0.04 to 0.22)
TG, mmol/L	0	−0.16 (−0.28 to −0.04)	−0.31 (−0.53 to −0.09)	−0.37 (−0.60 to −0.13)	−0.41 (−0.64 to −0.17)	−0.44 (−0.67 to −0.22)	−0.47 (−0.69 to −0.26)	−0.50 (−0.72 to −0.28)	−0.53 (−0.76 to −0.31)	−0.56 (−0.86 to −0.31)
SBP, mmHg	0	−2.37 (−6.99 to −2.34)	−4.59 (−8.21 to −0.97)	−5.44 (−9.41 to −1.47)	−6.17 (−9.87 to −2.12)	−6.86 (−10.80 to −3.12)	−7.56 (−10.98 to −3.29)	−8.25 (−12.0 to −4.25)	−8.95 (−12.25 to −4.5)	−9.64 (−12.6 to −6.7)

[1] The results are from a random-effects meta-analysis. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

results from studies with a low risk of bias are reported in Table 1. No other subgroup difference was seen in terms of risk of bias.

Publication bias

Supplemental Figures 32–46 indicate the assessment of the funnel plot asymmetry. There was some evidence of asymmetry in the funnel plot for LDL cholesterol at the 6-month follow-up and for HDL cholesterol at the 12-month follow-up, though Egger's tests were not significant ($P > 0.05$). There was also asymmetry in the funnel plot for body weight at the 12-month follow-up, which was confirmed by Egger's test ($P = 0.04$).

Grading the evidence

Supplemental Table 22 presents the GRADE evidence table for primary and secondary outcomes across 3 time periods. At the 6-month follow-up, the certainty of the evidence was graded high for most outcomes due to upgrades for significant dose-dependent effects. The effect of carbohydrate restriction surpassed thresholds set as MCIDs for HbA1c (0.50%), body weight (4.4 kg), LDL cholesterol (0.10 mmol/L), TG (0.09 mmol/L), and SBP (2 mmHg). There was also evidence of a significant dose-dependent effect on FPG, but the effect size did not surpass the MCID threshold (1.60 mmol/L). The evidence was rated moderate for total cholesterol due to a downgrade for imprecision, and was rated low for HDL cholesterol due to downgrades for inconsistency and imprecision.

At the 12-month follow-up, the evidence was rated low to moderate for FPG, HDL cholesterol, LDL cholesterol, SBP, and total cholesterol due to various downgrades for imprecision, inconsistency, and publication bias. The certainty of the evidence was rated as high for HbA1c and TG and as moderate for body weight, wherein there were significant dose-dependent effects. The effect sizes did not surpass MCID thresholds for any outcomes. At follow-ups longer than 12 months, the only dose-dependent effect was for HbA1c, where the certainty of the evidence was rated low. The between-reviewer agreement for GRADE ratings were near perfect (Cohen's kappa = 0.90) for high-certainty evidence, substantial (Cohen's kappa = 0.78) for moderate-certainty evidence, and moderate for low- and very-low-certainty evidence (Cohen's kappa = 0.58 and 0.52, respectively).

Discussion

This dose-response meta-analysis included 50 randomized trials, involving 4291 patients with type 2 diabetes, that evaluated the effects of carbohydrate-restricted diets (≤45%) on cardiometabolic outcomes when compared with low-fat diets or dietary advice. We indicated that each 10% decrease in carbohydrate intake can exert a significant reduction on levels of HbA1c; FPG; body weight; blood lipids, including LDL cholesterol and TG; and SBP at the 6-month follow-up. We indicated that there was an inverse linear association between the percentage of carbohydrate intake and levels of HbA1c, FPG, body weight, TG, and SBP at the 6-month follow-up, with the magnitude of the effect exceeding MCID thresholds for HbA1c, body weight, LDL cholesterol, TG, and SBP. Our dose-response

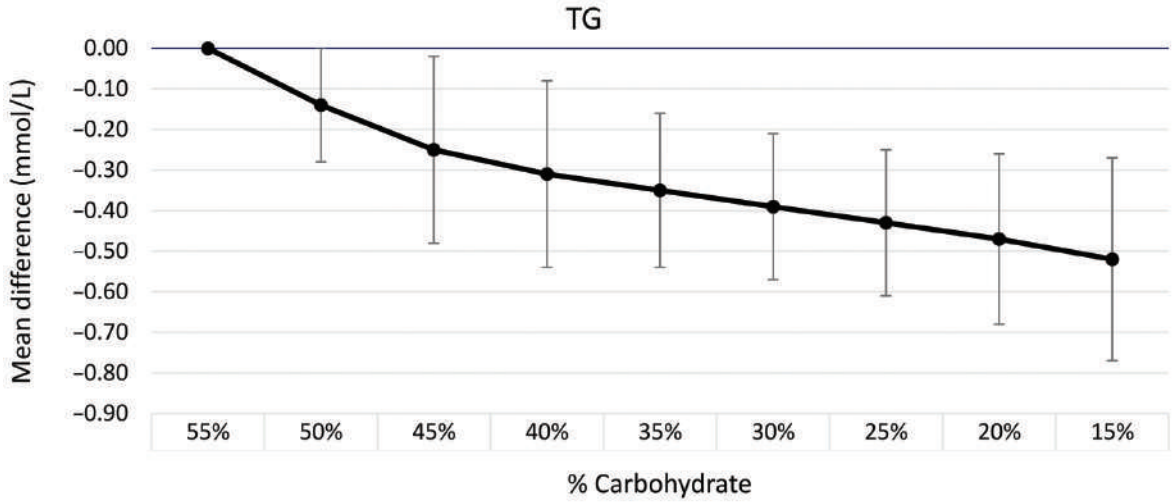

FIGURE 10 Dose-dependent effect of carbohydrate restriction on TG (mmol/L) in patients with type 2 diabetes at the 12-month follow-up ($n = 13$ trials). TG, triglyceride.

meta-analysis also indicated evidence of U-shaped effects on total cholesterol and LDL cholesterol at the 6-month follow-up and on body weight at the 12-month follow-up. At the 12-month follow-up, the effect of carbohydrate restriction was limited to reductions in HbA1c, body weight, LDL cholesterol, and TG, with the sizes of the effects well below MCID thresholds. At follow-ups longer than 12 months, carbohydrate restriction resulted in a significant but unimportant reduction in HbA1c.

The effectiveness of moderate-carbohydrate (45% to 26%), low-carbohydrate (25% to 11%), and very-low-carbohydrate (≤10%) diets for type 2 diabetes management has been evaluated in several meta-analyses of intervention studies. Our results are in line with those of previous reviews demonstrating the short-term effectiveness of restricted-carbohydrate diets in reducing HbA1c (5, 8–10, 14, 15, 18, 20, 22), body weight (8, 14, 15, 17, 18, 20, 22), serum TG (8–10, 15, 17, 19, 22), and blood pressure (9, 15), as well as in increasing HDL cholesterol (5, 8–10, 15, 18, 19).

For serum cholesterol, the results are inconsistent. Although most reviews indicated that there were no differences between low-carbohydrate diets and other diets, mostly low-fat diets, in reducing serum total cholesterol (5, 15, 17, 20, 22), a recent systematic review indicated a significant increase at the 6-month follow-up (14). However, our dose-response meta-analysis indicated a U-shaped effect for total cholesterol at the 6-month follow-up, with an upward curve at carbohydrate intakes less than 40%. There was also a slight upward curve for LDL cholesterol at carbohydrate intakes less than 35% at the 6-month follow-up. The null findings observed in previous reviews can be explained by the U-shaped effect, where serum total cholesterol increased at carbohydrate intakes lower than 40%. The intake of dietary fat increases along with the decrease in carbohydrate intake, and this can partly explain the U-shaped effect observed in the dose-response analysis.

Although dose-response meta-analyses suggested an upward curve at carbohydrate intakes of 40% for total cholesterol and 35% for LDL cholesterol at the 6-month follow-up, the sizes of the effects did not surpass the null effect and remained protective, indicating that low- and very-low-carbohydrate diets still decrease blood lipids as compared to a carbohydrate intake of 65%. However, due to increases in fat intake, the effects of low-carbohydrate diets in reducing blood lipids diminished. Indeed, the type of fat used to replace carbohydrate intake has an important effect on serum lipids; thus, replacing carbohydrate with SFAs, PUFAs, and/or MUFAs may have diverse effects.

A recent study-level meta-analysis of 8 European studies indicated that replacement of dietary carbohydrates with fats had favorable effects on serum lipids when fats were consumed in the forms of MUFAs and PUFAs but not in the form of SFAs (94). Another meta-analysis of randomized trials by the WHO suggested that replacement of dietary carbohydrate with SFAs had unfavorable effects on serum lipid profiles (95). Of 23 trials with carbohydrate intakes < 40% (the nadir of the curve of total cholesterol at 6 months) in the intervention arm in the present review, 9 trials reported changes in subtypes of dietary fats from baseline to the end of the study (48–51, 53, 58, 59, 77, 88). Of those, 5 trials reported an increase in SFA intakes during the intervention period (49, 58, 59, 77, 88), and 4 trials reported a decrease in PUFA intakes (48, 50, 53, 88).

With regards to the type of dietary protein, increasing the consumption of plant-based proteins (96) and substituting plant-based proteins for animal-based proteins (97) could improve serum lipid profiles. However, trials included in the present review did not report sufficient information about potential changes in the consumption of subtypes of dietary protein over the intervention duration.

There was also a U-shaped effect on body weight at the 12-month follow-up, with an upward curve at a carbohydrate intake less than 35%. The U-shaped effect may be due to a decrease in adherence to the prescribed diets, along with the increase in the degree of carbohydrate restriction. Our U-shaped effect was consistent with the results of a recent meta-analysis of randomized trials demonstrating trivial and nonsignificant effects of low-carbohydrate diets (<26%) on body weight at the 12-month follow-up (8). However, the analysis of TG indicated a somewhat opposite finding, where there was a linear reduction

in TG at the 12-month follow-up, which was consistent with the previous meta-analysis (8).

Favorable effects of carbohydrate-restricted diets in improving cardiometabolic outcomes in patients with type 2 diabetes can be attributable to their effects on reducing hunger, pancreatic and hepatic fat content, insulin resistance, pancreatic beta-cell work, and glucotoxicity, as well as to a reduction in ad libitum energy intake (40). Furthermore, in the subgroup analyses based on whether or not trials implemented calorie-matched controls, based on data from 39 trials, we did not find significant subgroup differences, suggesting that favorable effects of low-carbohydrate diets are partly mediated by other mechanisms, such as increasing energy expenditure (98).

Our results indicated that the favorable effects of carbohydrate restriction on cardiometabolic outcomes were not maintained (for FPG, SBP, HDL cholesterol, and total cholesterol) or diminished substantially (for HbA1c, LDL cholesterol, TG, and body weight) at follow-ups longer than 6 months. Although we observed significant and important (larger than MCID thresholds) effects on levels of HbA1c, body weight, LDL cholesterol, TG, and SBP at the 6-month follow-up, the effects of carbohydrate restriction did not surpass the MCID thresholds set for any outcomes at longer follow-up durations. The remarkable reduction in the benefits of restricted-carbohydrate diets on type 2 diabetes management was consistently reported in previous reviews (5, 10, 14, 15, 17, 19, 20, 22), and may be attributable to the decrease in the degree of adherence to low-carbohydrate diets (8, 99).

Our prespecified subgroup analyses suggested evidence of a significant effect modification by the percentage of protein intake in the intervention arms, where trials that implemented a low-carbohydrate and moderate- to high-protein diet (>20%) indicated greater reductions in FPG and body weight as compared to trials with low-protein diets (≤20%) at the 6-month follow-up. We also observed greater reductions in HbA1c and TG at the 6-month follow-up in trials that implemented a moderate- to high-protein diet, though tests for subgroup differences were not significant. There is evidence that high-protein diets may exert a beneficial effect on glycemic control as compared to low-protein diets (100–102). However, a previous meta-analysis of 15 RCTs with follow-ups longer than 12 months indicated that high-protein (≥25%), low-fat (<30%) diets were not superior to low-protein (≤20%), low-fat (<30%) diets in reducing levels of cardiometabolic outcomes in adults (38). We also did not find evidence of a significant effect modification by protein intake at follow-ups longer than 6-month.

With regards to the percentage of protein in the intervention arms, we found greater reductions in FPG and HbA1c at the 6-month follow-up in trials implementing 20% to 25% protein as compared to those with <20% and ≥25% protein intakes. This may be due to the fact that some participants may have difficulty eating enough to maintain isocaloric conditions while assigned to high-protein diets (≥25%), as these diets may have high content of saturated fats from animal-based proteins (103). However, the analyses of body weight and serum TG indicated somewhat opposite findings, where greater reductions were seen at the 6-month follow-up in trials that implemented ≥25% protein as compared to those with <20% and 20% to 25% protein intakes. In addition, the analyses of other outcomes did not indicate any significant effect modifications by the percentage of protein in the intervention program either at the 6-month or at 12-month follow-ups.

Clinical implications

Traditional pairwise comparisons used in standard meta-analyses (4–10, 12, 14–22) are profoundly limited in their ability to determine the optimum dose of intervention and, thus, to provide the best evidence needed for decision-making. Although the short-term effectiveness of carbohydrate-restricted diets on type 2 diabetes management has been established (8, 15), the optimum carbohydrate intake has not been yet determined. A recent network meta-analysis of RCTs indicated that low-carbohydrate (≤25%) and moderate-carbohydrate (45% to 26%) diets were both effective in reducing HbA1c levels when compared with a conventional low-fat diet; however, there was not a significant difference between low- and moderate-carbohydrate diets (13). Another network meta-analysis also indicated similar nonsignificant differences for blood lipids (11). However, the previous network meta-analysis included only 20 randomized trials in the analyses of carbohydrate-restricted diets, compared with 50 trials included in the present review. To our knowledge, no systematic review of intervention studies has evaluated the dose-dependent effects of carbohydrate restriction in patients with type 2 diabetes. In the present meta-analysis, using a novel statistical approach, we indicated that levels of HbA1c, FPG, body weight, TG, and SBP decreased proportionally with the decrease in carbohydrate intake at the 6-month follow-up.

In addition, in contrast to previous reviews indicating null effects on total cholesterol and LDL cholesterol, we found an interesting U-shaped effect, with the greatest reductions at 40% for total cholesterol and 35% for LDL cholesterol. We also indicated that even a modest (10%) decrease in carbohydrate intake can exert significant improvement in cardiometabolic outcomes, with higher restriction indicating more favorable effects. A 10% decrease in carbohydrate intake, which is equal to 50 g/d in a 2000-kcal/d diet, can be easily used to develop simple and easy-to-understand messages for use in patients with type 2 diabetes.

We had no evidence regarding the effects of very-low-carbohydrate diets (≤10%). A recent systematic review indicated that trials with a very-low-carbohydrate diet (≤10%) and with highly adherent patients reported greater weight loss in comparison with low-carbohydrate diets (26% to 11%) at the 6-month follow-up (8). However, due to insufficient data regarding carbohydrate percentages in either the intervention or control groups we were unable to include very-low-carbohydrate or ketogenic diets in our dose-response meta-analysis. In addition, according to current recommendations, very-low-carbohydrate diets are generally defined as diets with ≤10% or <50 g/d carbohydrate intakes (31, 32). Of 11 trials that implemented a very-low-carbohydrate diet (based on a carbohydrate intake <50 g/d) in the recent meta-analysis (8), 1 trial was not included in the present meta-analysis because did not report sufficient information regarding the percentage of carbohydrate intake in the control group (104), and the other 10 trials (included in the present review) were classified as having low-carbohydrate diets when we converted self-reported carbohydrate intakes to % calorie (49, 50, 52, 58, 61, 77, 79, 80, 83, 89). For example,

in 1 trial that evaluated the effect of a prescribed ketogenic diet (20 g/d) on cardiometabolic outcomes, the percentage of carbohydrate intake was 13% of the total calorie intake over the follow-up period when we looked at the self-reported dietary data (89).

Strengths and limitations of the study

Given a large number of published meta-analyses (4–22), a recent narrative review suggested that further systematic reviews evaluating the effects of low-carbohydrate diets in patients with type 2 diabetes should be highly discouraged unless they consider some important issues not addressed in the previously published meta-analyses (40). The present meta-analysis provided novel insights into the dose-dependent effects of carbohydrate restriction on cardiometabolic outcomes in patients with type 2 diabetes, that were not presented in the previously published meta-analyses (4–22). We evaluated the certainty of evidence using the GRADE approach, used MCID thresholds that were set for use in patients with type 2 diabetes (8), and determined the degrees of carbohydrate restriction at which the effect sizes surpassed thresholds set as indicating an important effect. Whenever possible, we used self-reported dietary data for the analyses. One of the main problems in implementing low-carbohydrate diets is that it is relatively hard to completely adhere to prescribed carbohydrate restrictions (40). Previous meta-analyses did not consider the differences between prescribed and actual carbohydrate intakes, and only performed a sensitivity analysis restricting the analyses to participants with high adherence to the prescribed diets (8). Although self-reported dietary intakes are subject to measurement error, especially in trials wherein participants are not blinded (105, 106), they can present more accurate information about the amounts of carbohydrate intake in the trials than can prescribed data (40). We converted g/d to % calorie, and thereby harmonized the data across trials. We included sufficient trials for dose-response meta-analyses for both moderate-carbohydrate (39 trials) and low-carbohydrate (10 trials) diets.

Our meta-analysis was also accompanied by some limitations. Our main limitation is that, due to inadequate information, we had insufficient evidence on very-low-carbohydrate diets ($\leq$10%). We had only 1 trial with 10% carbohydrate intake in our analyses (80). A dose-response meta-analysis needs percentage of carbohydrate intake in both the intervention and control groups; therefore, some important trials without such information (107–111) were not included in the analyses. Second, there might be other differences than carbohydrate intakes in the intervention and control groups in each trial, and this may partially affect the results. In addition, the quality of the diets, especially of dietary carbohydrates, was not consistent across study arms in the trials. There is evidence that diets with equal amounts of carbohydrates and different glycemic indexes may exert different effects on cardiometabolic risk factors (90). A recent systematic review of randomized trials indicated that diets with a low glycemic index can exert small but important improvements in cardiometabolic risk factors in patients with diabetes (112). However, we had limited evidence to evaluate the potential effects of carbohydrate quality on the results. Third, according to our a priori protocol (29), we did not evaluate adverse events in our review. Previous reviews have reported no significant or clinically important increases in adverse events following adherence to low-carbohydrate diets at 6-month and 12-month follow-ups (8, 14). However, the long-term effects of such diets on cardiovascular and renal diseases have not been evaluated. Our subgroup analysis indicated a significant decrease in HDL cholesterol in trials without exercise at the 12-month follow-up; however, this decrease was not clinically important. Fourth, there was high heterogeneity in the data in the analyses of FPG, LDL cholesterol, SBP, total cholesterol, and body weight at the 6-month follow-up, and in the analyses of FPG, HDL cholesterol, SBP, TG, and total cholesterol at the 12-month follow-up. We did several subgroup analyses based on participant, intervention, and comparator characteristics; however, the observed heterogeneity in the data remained largely unexplained. The forest plots indicated that most of the trials (>75%) included in the analyses were in the same direction; thus, the large heterogeneity in the data is mainly due to the difference in the magnitude (weak, moderate, or strong) of the effects rather than a difference in the direction (decreasing or increasing) of the effects. The exceptions were FPG and TG at the 12-month follow-up, where there were variations in the direction of the effects. In addition, there are several other differences across trials, including the duration and severity of diabetes, medication used, degree of adherence to dietary interventions, and quality of carbohydrates, that may result in large differences across trials. Fifth, generally, low-carbohydrate diets are also low caloric; thus, it may be difficult to disentangle the decline in carbohydrate intake from the decline in energy intake. We did subgroup analyses based on the presence of calorie restrictions (yes or no) and calorie-matched controls (yes or no) in the trials. We found that the results in the subgroup of trials without calorie restrictions and in those with calorie-matched controls were the same as in the main analyses in almost all analyses. The exceptions were serum TG at the 6-month follow-up and body weight at the 12-month follow-up, where studies with calorie restrictions indicated significantly stronger effects than trials without calorie restrictions. These findings suggests that restricting carbohydrate intake, independent of calorie restriction, can still exert significant improvement in levels of cardiometabolic risk factors. However, of 50 trials included in the present meta-analysis, only 16 trials (32%) did not implement calorie restrictions in their intervention programs, most of which were moderately restricted carbohydrate diets. Therefore, we have limited evidence to disentangle the decline in carbohydrate intake from the decline in energy intake for very-low-carbohydrate diets.

Conclusions

To conclude, the present dose-response meta-analysis provided novel information about the dose-dependent effects of carbohydrate restriction in patients with type 2 diabetes. Carbohydrate restriction can exert significant and important improvements in cardiometabolic outcomes at short-term follow-ups. We indicated that there were inverse linear associations between carbohydrate percentages and levels of HbA1c, FPG, body weight, TG, and SBP at the 6-month follow-up, with the magnitudes of the effects exceeding MCID thresholds for HbA1c, body weight, LDL cholesterol, TG, and SBP. There was evidence of U-shaped effects on total cholesterol and LDL cholesterol at the 6-month follow-up and on body weight at the

12-month follow-up. The favorable effects of low-carbohydrate diets diminished remarkably at the 12-month follow-up and were not maintained at follow-ups longer than 12 months. Further well-designed trials are needed to address the impacts of very-low-carbohydrate diets (≤10%) in patients with type 2 diabetes.

The authors' responsibilities were as follows – AJ, SS-B: conceived and designed the study, conducted the systematic search, read the full texts for eligibility, evaluated trials for risk of bias; SZ-M, BJ, HS, AM: screened articles; AJ, SZ-M: extracted data from original trials; AJ: performed the analyses and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted; AJ, SZ-M, BJ, YH, ATJ, SZ-M, HS, AM, FH: contributed to the interpretation of the results and wrote the first draft of the manuscript; SS-B: contributed to the interpretation of the results, critically revised the manuscript, and is the guarantor; all authors: acknowledge full responsibility for the analyses and interpretation of the report and read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon reasonable request.

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