REVIEW

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Comparative effects of different macronutrient compositions for type 2 diabetes management: a systematic review and network meta-analysis of randomized trials

Negin Badrooj¹, Ahmad Jayedi² and Sakineh Shab-Bidar^{1*}

Abstract

Background To assess and rank the comparative effects of different exact macronutrient compositions for type 2 diabetes management rather than examining single macronutrients or as a dietary pattern.

Methods PubMed, Scopus, and Cochrane Library Central Register of Controlled Trials were searched. Randomized controlled trials were included. A random-effects network meta-analysis with a Bayesian framework was performed to calculate the mean difference (MD) and 95% credible intervals (CrIs). The certainty of evidence was rated using the GRADE approach.

Results 80 trials with 9232 patients with type 2 diabetes were included in the network meta-analysis. A very lowcarbohydrate, high-protein, and calorie-restricted diet had the greatest effect on reducing HbA_{1c} (range of mean difference: -1.0% to -1.79%), weight (range of mean difference: -5.83 kg to -10.96 kg), and FPG (range of mean difference: -2.20 mmol/L to -2.88 mmol/L) at 6-month follow-up, but at 12-month follow-up, the effect remained only for HbA_{1c} (range of mean difference: -1.25% to -1.30%) and FPG (range of mean difference: -1.21 mmol/L to -1.27 mmol/L). For weight loss in 12-month follow-up, the low-carbohydrate, high-protein diet was probably the most effective approach (range of mean difference: -10.05 kg to -14.52 kg). The best dietary approach to reduce LDL at 6-month follow-up was a low carbohydrate, high protein, calorie-restricted diet (range of mean difference: -0.49 mmol/L to -0.59 mmol/L) and at 12-month follow-up, a moderate carbohydrate, standard protein, calorierestricted diet was effective in reducing LDL (mean difference: -0.87 mmol/L, 95%Crl -1.55 to -0.16).

Conclusions A very low carbohydrate, high protein, calorie-restricted diet can be an effective dietary composition in managing diabetes, but milder dietary carbohydrate restriction for weight loss in the long-term, and improving lipid profiles is needed.

Keywords Diet composition, Macronutrient composition, Network meta-analysis, Systematic review, Type 2 diabetes

*Correspondence:

Sakineh Shab-Bidar

s_shabbidar@tums.ac.ir

¹ Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P. O. Box 14155/6117, Tehran, Iran

² Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK

Introduction

Type 2 diabetes is a common and progressive disease characterized by beta cell dysfunction and insulin resistance [1, 2]. Diabetes is a major public health problem so 537 million adults suffer from this chronic disease in the world [3]. Nutritional therapy, as one of the components of behavioral support, plays a vital role in the



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management of diabetes [4]. Despite the agreement on nutrition recommendations provided by scientific institutes [2, 5–7], there is still confusion and controversy regarding the optimal ratio of carbohydrate, fat, and protein intake for most people with type 2 diabetes.

Regarding carbohydrate restriction, a dose-response meta-analysis showed that a 10% decrease in carbohydrate intake can significantly reduce glycemic levels at the 6-month follow-up in patients with type 2 diabetes. However, these observed effects weakened or disappeared at follow-up beyond 6 months. Also, a U-shaped effect was observed for total cholesterol and LDL cholesterol, so the greatest reduction in these indicators was observed in the amount of 40% carbohydrates [8]. About the optimum duration of carbohydrate restriction, findings from a recent meta-analysis study suggest the effectiveness of long-term low-carbohydrate diets in improving dyslipidemia in people with type 2 diabetes but do not recommend long-term low-carbohydrate diets for blood glucose control [9]. A recent meta-analysis found that the ketogenic diet, which is associated with severe carbohydrate restriction, may improve lipid profiles but does not provide additional benefits for glycemic control or weight loss for patients with type 2 diabetes [10]. The results of a network meta-analysis showed that energy, carbohydrate, and dietary glycemic index (GI) restriction were the most effective approaches to improve diabetes-related outcomes [11]. However, this study did not fully examine the interventions in detail. For example, if it states that calorie restriction is the best way for weight reduction, it does not provide the reader with information about how macronutrients are distributed in this calorie-restricted diet. A recent study on calorie restriction showed that restricting energy intake to 900 kcal/day resulted in significant reductions in muscle mass, suggesting that less restrictive interventions may be preferable [12]. Another network meta-analysis in this field showed that the ketogenic diet, Mediterranean diet, moderate-carbohydrate diet, and low glycemic index diet were effective options for controlling HbA1c and fasting glucose in patients with diabetes [13]. A recent network meta-analysis also showed that the most effective dietary intervention for improving blood glucose was following the Mediterranean diet, and a low-carbohydrate diet was the best approach for improving anthropometric indices in patients with type 2 diabetes [14].

Following our previous dose–response study, which showed that the greatest reduction in total cholesterol and LDL was observed in the amount of 40% carbohydrates [8], we decided to investigate other effective factors in addition to the amount of carbohydrates, such as calorie restriction status and protein intake, in improving the indicators related to diabetes. Despite many studies in the field of nutritional management of type 2 diabetes, there is no single ratio of carbohydrate, fat, and protein intake that is optimal for every person with type 2 diabetes. To fill the existing gap and further exploration, we aimed to undertake a systematic review and network meta-analysis of randomized trials to assess the comparative effect of different macronutrient compositions for type 2 diabetes management.

Methods

This network meta-analysis was conducted per instructions outlined in the Cochrane Handbook for Systematic Reviews of Interventions [15] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook [16]. The protocol of the study was registered with PROSPERO (CRD42023473360) [17].

Outcomes

The primary outcome was a change in glycated hemoglobin (HbA_{1c}, %), while secondary outcomes were changes in body weight (kg), fasting plasma glucose (FPG, mmol/L), and low-density lipoprotein (LDL) cholesterol (mmol/L), As per our protocol [17].

Systematic search

PubMed, Scopus, and Cochrane Library Central Register of Controlled Trials were searched from inception until May 2023. The complete search strategy, including the Cochrane recommended filter for the identification of randomized trials in PubMed [18], is provided in (Additional file 1: Table S1). Two authors (NB and AJ) independently screened titles and abstracts. Then, these reviewers independently read the full texts of all potentially relevant articles and screened the reference lists of meta-analyses in this field to find relevant studies.

Study selection

We used the PICOS framework (Population, Intervention/exposure, Comparator, Outcomes, and Study design) to determine eligibility criteria. The eligible studies needed to meet the following four inclusion criteria: (1) randomized controlled trials, with a minimum intervention period of 4 weeks, conducted in adults with existing type 2 diabetes, with or without cardiovascular conditions and regardless of medication use or glucose concentration and HbA_{1c} level, aged 18 years or older; (2) evaluated the effects of a diet with prespecified macronutrient composition (%carbohydrate and %protein), with or without calorie restriction status, having behavioral support and structured physical activity, against a control diet; (3) considered change in body weight, HbA_{1c} , fasting plasma glucose (FPG), and LDL cholesterol as the outcome of interest; (4) provided mean and standard

Page 3 of 15

deviation (SD) of change in aforementioned outcomes or reported sufficient information to estimate those values; and (5) provided amount of macronutrients intake (percentage energy or grams per day) in both intervention and control groups.

Eligible control groups will include waitlist controls or any active controls including competing dietary programs with or without exercise, or lifestyle and behavioral recommendations. All outcomes will be assessed separately across three time periods including 1 to ≤ 6 months (6 months), 6 to ≤ 12 months (12 months), and > 12 months. However, due to the limited number of studies that reported enough information for the analyses (n < 10), we could not perform network meta-analysis at follow-up longer than 12 months.

Screening and data extraction

From each trial, the following characteristics: The last name of the first author, year of publication, number of participants, mean age, baseline body mass index and HbA1c concentration, duration of diabetes, % female, intervention and comparator characteristics, study design (parallel or cross-over), duration of intervention, calorie restriction status, having behavioral support and structured physical activity, and mean and corresponding SD of change from baseline values in each study arm were extracted independently by two reviewers (NB and AJ).

Risk of bias (quality) assessment

Risk of bias of included trials was assessed independently by two authors (NB and AJ) per guidance outlined in version 2.0 of the Cochrane tool for risk of bias assessment [19]. Disagreements were resolved through consensus.

Classification of dietary programs based on macronutrient composition

We used the following thresholds to classify dietary interventions based on carbohydrate and protein intake. Based on carbohydrate intake, we classified diets as high carbohydrate (>45% or 230 gr/d), moderate carbohydrate (26–45% calorie intake or 130–230 gr/day), low carbohydrate (11–26% or 50–130 gr/d), and very low carbohydrate intake ($\leq 10\%$ or 50 gr/day) [20, 21]. We also used the following thresholds for protein intake: standard protein (<15%), moderate protein (15–25%), and high protein (>25%) [22, 23]. Then, we named dietary interventions as calorie-restricted for trials that implemented a pre-specified calorie-restricted diet.

Data synthesis and analysis

We selected mean differences and their 95% credible intervals (CrIs) as effect sizes for reporting the results of our network meta-analysis. The mean and SD of change in primary and secondary outcomes from baseline were calculated to perform the analyses. If our required values were not reported in clinical trials included in our study, we used the Cochrane Handbook guidance to calculate these values [19].

A random-effects pairwise meta-analysis with a Bayesian framework was performed to estimate direct estimates [24, 25] and node-splitting to evaluate the inconsistency between direct and indirect evidence [26]. We used a network meta-analysis carried out by a random-effect model within a Bayesian framework to calculate network estimates [24, 25]. The surface under the cumulative ranking curves (SUCRA) was also incorporated in our analysis for ranking probabilities. Both pairwise and network meta-analyses were performed under the *gemtc* package [27] of R version 3.4.3 (R Studio, Boston, MA) [28].

Two pre-specified sensitivity analyses were performed with trials that were conducted on participants with overweight or obese and also those with a low risk of bias [29]. To evaluate the potential for intransitivity, the distribution of the potential effect modifiers across the available direct comparisons was assessed [15]. Mean age, baseline HbA_{1c}, percentage of female participants, and duration of type 2 diabetes were considered potential effect modifiers (Additional file 1: Figs. S1–S4). Comparison-adjusted funnel plots were created to assess the potential for publication bias (Additional file 1: Figs. S5– S12) [30].

Grading of the evidence

We assessed the certainty of evidence using the GRADE approach developed for network meta-analyses [31]. To rate for imprecision, a minimally contextualized approach was used, which, instead of considering the magnitude of the observed effects, only considers whether the CrIs meet the minimal clinically important difference (MCID) threshold [32]. This method does not rely on statistical significance as the only indicator to determine the efficacy of the intervention because statistical significance has limitations and is not enough to determine the clinical relevance of intervention effects in clinical research. [33]. The MCID thresholds for primary and secondary outcomes were defined as 0.50% for HbA1c, 4.4 kg for body weight, 1.60 mmol/L for FPG, and 0.10 mmol/L for LDL cholesterol [34]. To assess the importance of the magnitude of network estimates, MCID thresholds, and effect size categories were used based on GRADE guidelines [35] as follows: large effect = \geq 5xMCID, moderate effect = \geq 2xMCID, small but important effect = ≥ 1 xMCID, and trivial/unimportant effect < 1 MCID [36].

Results

Literature search and study selection process

As described in Additional file 1: Fig. S13, the initial database and reference lists search identified 10,285 records. After excluding 2945 duplicates and 7058 irrelevant articles based on screening of the title and abstract, 282 full-texts were carefully reviewed for eligibility. A total of 80 articles were found that provided enough desirable information and were considered eligible to be included in this network meta-analysis. The list of studies excluded via full-text assessment with reasons for exclusions is provided in Additional file 1: Table S2.

Characteristics of primary trials included in the network meta-analysis

Additional file 1: Table S3 presents the general characteristics of 80 primary trials with 9232 patients with type 2 diabetes that were included in the network meta-analysis [37–116]. The median intervention duration was 24 weeks (range: 4–192 weeks), with 16 trials shorter than 12 weeks [38, 54-57, 62, 83, 84, 87, 92, 94, 95, 98, 102, 104, 107]. The median sample size was 61 participants (range: 8-2326 participants). Of the included trials, 35 were conducted exclusively in adults with overweight and obesity (BMI $\ge 25 \text{ kg/m}^2$) [37–42, 44, 45, 49–53, 57–59, 61, 62, 66–71, 75–77, 80–93, 96, 97, 99, 100, 103, 105-107, 110, 112, 114]. 12 trials had cross-over design [54-56, 72, 87, 94, 95, 102, 104, 105, 108, 111] and other trials had parallel design. 11 trials was conducted on patient without any hypoglycemic medication [37, 47, 52, 54, 65, 77, 78, 82, 84, 87, 113], 32 trials excluded patient treated with insulin [38, 39, 41, 42, 46, 50, 51, 55–59, 61, 68, 69, 71, 72, 74, 80, 85, 90, 94, 95, 99, 100, 104-108, 111, 114] and 35 trials included insulin-dependent patients with diabetes [40, 43-45, 48, 49, 53, 60, 62-64, 66, 67, 70, 73, 75, 76, 79, 81, 86, 88, 89, 92, 93, 96-98, 101-103, 109, 110, 112, 115, 116]. Of the trials, 55 implemented behavioral support [37-42, 44, 45, 47, 49, 51-53, 58-60, 63-70, 73-77, 79–83, 85, 87, 88, 91, 93–97, 99–103, 106, 109–114], 53 implemented calorie restriction [39-42, 44-46, 49, 50, 52, 53, 57, 58, 60-62, 65, 66, 68, 70, 71, 74-77, 79, 80, 82-90, 92, 93, 96-101, 103, 105-107, 110, 112, 114-116], and 22 implemented supervised or structured exercise programs [37, 38, 42, 44, 47, 50-52, 59, 64, 67, 76, 80, 84, 86, 91, 93, 103, 106, 110, 114, 116]. Twentythree trials were rated to have a high risk of bias [40, 42, 50, 53, 55, 57, 61, 63, 65-67, 72, 74, 75, 86, 89, 90, 93–95, 102, 111, 112] and the risk of bias were rated to have some concerns for other fifty-seven trials (Additional file 1: Tables S4–S5).



Fig. 1 Network diagram showing the comparative effects of different dietary compositions on HbA1 $_c$ at 6-month

Primary outcome

Comparative effects of different dietary compositions on HbA_{1c} at 6-month are indicated in Fig. 1 and Table 1. The results suggested evidence of moderate certainty that a very low carbohydrate, high protein, calorie-restricted diet was effective in reducing HbA1c when compared with a wide range of other dietary programs (range of mean difference: - 1.0% to - 1.79%; Table 1). There was also moderate certainty of evidence that a low carbohydrate, moderate protein, calorierestricted diet was effective in reducing HbA1c when compared with other dietary programs (range of mean difference: - 0.65% to - 1.20%; Table 1). Low carbohydrate, high protein, calorie-restricted diet was also effective in reducing HbA_{1c} when compared with other dietary programs (range of mean difference: - 0.79% to -1.12%, GRADE = moderate; Table 1).

At 12-month (Fig. 2), there was evidence that very low carbohydrate diet, high protein, calorie-restricted diet was effective in reducing HbA_{1c} when compared with moderate carbohydrate, moderate protein diet (mean difference: – 1.25%, 95%CrI: – 2.43, – 0.01; GRADE=moderate) and high carbohydrate, moderate protein diet (mean difference: – 1.30%, 95%CrI: – 2.37 to – 0.28; GRADE=moderate) (Additional file 1: Table S6). Other dietary programs were not effective at 12-month follow-up.

Secondary outcomes

Comparative effects of different dietary compositions on body weight at 6-month are indicated in Table 2. The results suggested evidence of moderate certainty that a very low carbohydrate, high protein, calorie-restricted

| VLC-HP-CR | | | | | | | | | | | | | | | | | |
|-------------------------|-------------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|----------|
| -0.6 (-1.19, 0.06) | LC-MP-CR | | | | | | | | | | | | | | | | |
| -0.68 (-1.47, 0.1) | -0.08 (-0.95, 0.7) | LC-HP -CR | | | | | | | | | | | | | | | |
| -0.6 (-1.87, 0.56) | 0 (-1.28, 1.08) | 0.07 (-1.25, 1.32) | VLC-MP | | | | | | | | | | | | | | |
| -0.26 (+2.82, 2.25) | 0.33 (-2.22, 2.82) | 0.42 (-2.16, 2.95) | 0.35 (+2.31, 2.99) | VLC-HP | | | | | | | | | | | | | |
| -0.78 (-2.3, 0.74) | -0.19 (-1.7, 1.29) | -0.10 (-1.73, 1.53) | -0.17 (-1.92, 1.65) | -0.52 (-3.38, 2.38) | VLC-MP-CR | | | | | | | | | | | | |
| -1 (-1.88, -0.22) | -0.41 (-1.26, 0.28) | -0.33 (-1.29, 0.56) | -0.40 (-1.29, 0.49) | -0.75 (-3.25, 1.76) | -0.23 (-1.81, 1.29) | MC-MP | | | | | | | | | | | |
| -1.25 (-2.08, -0.53) | -0.65 (-1.48, -0.02) | -0.57 (-1.39, 0.15) | -0.65 (-1.82, 0.51) | -1 (-3.48, 1.49) | -0.48 (-2.1, 1.08) | -0.25 (-1.02, 0.5) | MC-HP-CR | | | | | | | | | | |
| -1.28 (-3.07, 0.45) | -0.69 (-2.48, 1) | -0.60 (-2.38, 1.13) | -0.67 (-2.65, 1.28) | -1.02 (-3.96, 1.92) | -0.50 (-2.78, 1.7) | -0.27 (-2.03, 1.47) | -0.03 (-1.61, 1.55) | HC-HP | | | | | | | | | |
| -1.3 (-2.57, -0.15) | -0.7 (-1.99, 0.39) | -0.62 (-1.85, 0.51) | -0.69 (-2.2, 0.8) | -1.05 (-3.7, 1.62) | -0.52 (-2.4, 1.28) | -0.29 (-1.52, 0.91) | -0.05 (-1.01, 0.92) | -0.02 (-1.87, 1.83) | MC-SP-CR | | | | | | | | |
| -1.33 (-2.03, -0.72) | -0.74 (-1.42, -0.21) | -0.66 (-1.37, 0) | -0.73 (-1.86, 0.42) | -1.08 (-3.56, 1.41) | -0.56 (-2.13, 0.96) | -0.33 (-1.04, 0.39) | -0.08 (-0.61, 0.47) | -0.06 (-1.71, 1.62) | -0.04 (-1.11, 1.06) | MC-MP-CR | | | | | | | |
| -1.34 (-2.37, -0.4) | -0.74 (-1.78, 0.13) | -0.66 (-1.65, 0.25) | -0.73 (+2.07, 0.59) | -1.09 (-3.64, 1.49) | -0.56 (-2.3, 1.1) | -0.33 (-1.32, 0.65) | -0.09 (-0.74, 0.58) | -0.06 (-1.76, 1.66) | -0.04 (-1.06, 1) | -0.01 (-0.84, 0.82) | MC-SP | | | | | | |
| -1.40 (-2.09, -0.69) | -0.80 (-1.49, -0.17) | -0.72 (-1.63, 0.22) | -0.79 (-1.92, 0.45) | -1.13 (-3.66, 1.44) | -0.62 (-1.96, 0.73) | -0.39 (-1.12, 0.44) | -0.15 (-0.93, 0.76) | -0.11 (-1.87, 1.71) | -0.1 (-1.29, 1.23) | -0.06 (-0.77, 0.74) | -0.06 (-1.05, 1.04) | Routine Care | | | | | |
| -1.46 (-2.67, -0.43) | -0.86 (-2.06, 0.08) | -0.78 (-2.03, 0.3) | -0.86 (-2.27, 0.48) | -1.22 (-3.8, 1.36) | -0.69 (-2.52, 1.02) | -0.46 (-1.55, 0.56) | -0.21 (-1.24, 0.77) | -0.19 (-2.06, 1.66) | -0.16 (-1.58, 1.2) | -0.13 (-1.16, 0.82) | -0.12 (-1.36, 1.04) | -0.06 (-1.31, 0.99) | MC-HP | | | | |
| -1.46 (-2.25, -0.83) | -0.87 (-1.61, -0.35) | -0.79 (-1.62, -0.07) | -0.86 (-1.96, 0.18) | -1.22 (-3.65, 1.22) | -0.69 (-2.29, 0.8) | -0.46 (-1.08, 0.1) | -0.21 (+0.75, 0.27) | -0.19 (-1.85, 1.46) | -0.16 (-1.27, 0.88) | -0.13 (-0.64, 0.31) | -0.12 (-0.97, 0.66) | -0.07 (-0.9, 0.6) | 0 (+0.87, 0.87) | HC-MP | | | |
| -1.5 (-2.38, -0.71) | -0.90 (-1.79, -0.19) | -0.82 (-1.65, -0.07) | -0.89 (-2.12, 0.32) | -1.25 (-3.75, 1.27) | -0.72 (-2.38. 0.86) | -0.49 (-1.32, 0.34) | -0.25 (-0.63, 0.15) | -0.22 (-1.84, 1.41) | -0.2 (-1.07, 0.69) | -0.16 (+0.8, 0.46) | -0.16 (+0.7, 0.37) | -0.10 (-1.06, 0.75) | -0.04 (-1.07, 1.07) | -0.03 (-0.63, 0.61) | HC-SP | | |
| -1.66 (-2.54, 0.89) | -1.06 (-1.95, -0.37) | -0.98 (-1.87, -0.19) | -1.05 (-2.3, 0.16) | -1.41 (-3.93, 1.12) | -0.89 (-2.55, 0.69) | -0.65 (-1.52, 0.18) | -0.41 (-1.03, 0.2) | -0.38 (-2.07, 1.3) | -0.36 (-1.5, 0.76) | -0.33 (+0.89, 0.2) | -0.32 (-1.22, 0.55) | -0.26 (-1.23, 0.57) | -0.20 (-1.26, 0.91) | -0.20 (-0.83, 0.48) | -0.16 (-0.88, 0.53) | HC-MP-CR | |
| -1.79 (-2.76, -0.93) | -1.2 (-2.17, -0.41) | -1.12 (-2.08, -0.23) | -1.19 (-2.48, 0.1) | -1.54 (-4.09, 1.02) | -1.02 (-2.72, 0.61) | -0.79 (-1.72, 0.14) | -0.55 (-1.22, 0.16) | -0.52 (-2.23, 1.21) | -0.5 (-1.67, 0.69) | -0.46 (-1.15, 0.22) | -0.46 (-1.4, 0.49) | -0.40 (-1.44, 0.53) | -0.33 (-1.45, 0.86) | -0.33 (-1.05, 0.46) | -0.30 (-1.07, 0.48) | -0.14 (-0.94, 0.69) | HC-SP-CR |
| Significant effects a | are indicated in bo | old text. | | | | | | | | | | | | | | | |

Table 1 Comparative effects of structured dietary programs on HbA_{1C} (%) at 6-month

Significant circles are indicated in four texts. Abbreviations: C, earbolytate: P, potein, H, high: L, low; M, moderate; VL, very low; S, standard; CR, calorie r GRADE rating: very low; low; low; moderate: high.



Fig. 2 Network diagram showing the comparative effects of different dietary compositions on $HbA1_c$ at 12-month

diet effectively reduced body weight compared with a wide range of other dietary programs (range of mean difference: -5.83 kg to -10.96 kg). There was evidence that low carbohydrate, high protein, calorie-restricted diet was effective in reducing weight when compared with high carbohydrate, moderate protein, calorie-restricted diet (mean difference: -5.14 kg, 95%CrI: -9.71 to -0.45; GRADE=moderate). Low carbohydrate, moderate protein, calorie-restricted diet was also effective in reducing body weight when compared with high carbohydrate, moderate protein diet (mean difference: -4.57 kg, 95%CrI: -8.33 to -0.68; GRADE=moderate). There

was evidence that very low carbohydrate, moderate protein, calorie-restricted diet was effective in reducing body weight when compared with high carbohydrate, moderate protein, calorie-restricted diet (mean difference: -4.51 kg, 95%CrI: -7.88 to -1.14; GRADE = moderate).

At 12-month (Additional file 1: Table S7), the results suggested evidence of moderate certainty that a low carbohydrate, high protein diet was effective in reducing weight when compared with a wide range of other dietary programs (range of mean difference: -10.05 kg to -14.52 kg). Other dietary programs were not effective at 12-month follow-up in reducing weight.

Comparative effects of different dietary compositions on FPG at 6-month are indicated in Table 3. The results suggested evidence of moderate certainty that a very low carbohydrate, high protein, calorie-restricted diet was effective in reducing FPG when compared with other dietary programs (range of mean difference: -2.20 mmol/Lto - 2.88 mmol/L). There was moderate certainty evidence that very low carbohydrate, moderate protein, calorie-restricted diet was effective in reducing FPG when compared with other dietary programs (range of mean difference: -1.49 mmol/L to - 2.37 mmol/L). Low carbohydrate, moderate protein, calorie-restricted diet was also effective in reducing FPG when compared with high carbohydrate, moderate protein, calorie-restricted diet (mean difference: -1.51 mmol/L, 95%CrI -2.99 to-0.09; GRADE = moderate). There was evidence that low carbohydrate, high protein, calorie-restricted diet was effective in reducing FPG when compared with moderate carbohydrate, standard protein diet (mean difference:

Table 2 Comparative effects of structured dietary programs on body weight (kg) at 6-month

| VLC-HP-CR | | | | | | | | | | | | | | | | | |
|---------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|----------|
| -5.83 (-10.85, -0.98) | LC-HP-CR | | | | | | | | | | | | | | | | |
| -5.10 (-10.62, 0.27) | 0.74 (-4.67, 6.13) | LC-MP -CR | | | | | | | | | | | | | | | |
| -5.87 (+12.42, 0.63) | +0.05 (+6.44, 6.54) | -0.80 (-7.17, 5.84) | MC-HP | | | | | | | | | | | | | | |
| -6.16 (-12.57, 0.66) | -0.34 (-6.06, 5.95) | -1.08 (-7.79, 6.23) | -0.31 (-7.88, 7.76) | LC-HP | | | | | | | | | | | | | |
| -6.45 (-11.69, -1.32) | +0.63 (+5.39, 4.27) | -1.38 (-7.12, 4.54) | -0.58 (-7.46, 6.21) | -0.28 (-7.42, 6.3) | VLC-MP-CR | | | | | | | | | | | | |
| -6.95 (-9.83, -3.85) | -1.12 (-5.83, 4.03) | -1.85 (-7.25, 3.94) | -1.08 (-7.56, 5.7) | -0.78 (-7.45, 5.64) | -0.50 (-5.41, 4.78) | Routine care | | | | | | | | | | | |
| -6.60 (-15.43, 2.31) | -0.76 (-9.54, 8.23) | -1.50 (-10.27, 7.47) | -0.72 (-10.26, 8.85) | -0.44 (-10.46, 9.34) | -0.13 (-9.22, 9.04) | 0.34 (-8.64, 9.26) | VLC-HP | | | | | | | | | | |
| -6.98 (-13.07, -0.92) | -1.14 (-7.4, 5.28) | -1.89 (-8.73, 5.11) | -1.11 (+8.86, 6.69) | -0.81 (-8.56, 6.47) | -0.53 (-7.24, 6.27) | -0.03 (-5.97, 5.67) | -0.37 (-10.27, 9.46) | VLC-MP | | | | | | | | | |
| -8.37 (-12.26, -4.43) | -2.54 (-5.99, 1.18) | -3.28 (-7.47, 1.17) | -2.51 (-8.04, 3.18) | -2.20 (-8.13, 3.36) | -1.92 (-5.91, 2.28) | -1.42 (-5.53, 2.54) | -1.77 (-10.02, 6.45) | -1.39 (-7.09, 4.4) | MC-MP-CR | | | | | | | | |
| -8.01 (-12.4, -3.62) | -2.17 (-6.81, 2.61) | -2.92 (-8.3, 2.64) | -2.14 (-8.64, 4.4) | -1.83 (-8.29, 4.15) | -1.55 (-6.79, 3.74) | -1.06 (-5.19, 2.81) | -1.41 (-10.36, 7.44) | -1.03 (-5.26, 3.21) | 0.37 (+3.57, 4.18) | MC-MP | | | | | | | |
| -8.84 (-13.43, -4.24) | -3.0 (-7.43, 1.58) | -3.75 (-9.06, 1.69) | -2.96 (-9.4, 3.47) | -2.66 (-8.91, 3.12) | -2.38 (-7.53, 2.82) | -1.89 (-6.44, 2.4) | -2.23 (-11.13, 6.51) | -1.86 (-7.08, 3.35) | -0.46 (-4.21, 3.13) | -0.84 (-3.89, 2.24) | HC-HP | | | | | | |
| -9.12 (-13.44, -4.78) | -3.29 (-6.97, 0.59) | -4.02 (-8.64, 0.8) | -3.25 (-9.17, 2.72) | -2.95 (-8.5, 2.2) | -2.66 (-7.3, 2.09) | -2.17 (-6.63, 2.06) | -2.52 (-11.01, 5.88) | -2.14 (-7.84, 3.61) | -0.75 (-3.55, 1.99) | -1.11 (-4.95, 2.76) | -0.29 (-3.71, 3.22) | MC-HP-CR | | | | | |
| -9.97 (-17.10, -2.84) | -4.13 (-10.60, 2.47) | -4.87 (-12.23, 2.67) | -4.11 (-12.35, 4.19) | -3.81 (-11.25, 3.25) | -3.51 (-10.81, 3.88) | -3.03 (-10.26, 4.04) | -3.37 (-13.64, 6.8) | -2.98 (-10.97, 5.07) | -1.60 (+7.97, 4.72) | -1.96 (-8.71, 4.83) | -1.14 (-7.67, 5.45) | -0.85 (-6.84, 5.11) | MC-SP-CR | | | | |
| -9.8 (-15.40, -4.23) | -3.99 (+8.67, 0.97) | -4.73 (-10.59, 1.39) | -3.94 (-10.9, 3.1) | -3.64 (-9.62, 1.9) | -3.36 (-9.12, 2.57) | -2.86 (-8.51, 2.58) | -3.22 (-12.44, 5.98) | -2.83 (-9.42, 3.84) | -1.44 (+6.02, 3.06) | -1.81 (-6.86, 3.34) | -0.98 (-5.79, 3.95) | -0.70 (-4.7, 3.33) | 0.16 (-6.17, 6.50) | MC-SP | | | |
| -9.67 (-13.57, -5.81) | -3.85 (-7.59, 0.08) | -4.57 (+8.33, -0.68) | -3.8 (+9.06, 1.47) | -3.50 (-9.52, 2.08) | -3.22 (-7.57, 1.23) | -2.72 (-6.89, 1.21) | -3.08 (-11.1, 4.88) | -2.69 (+8.45, 3.04) | -1.30 (-3.33, 0.61) | -1.66 (-5.55, 2.2) | -0.84 (-4.54, 2.91) | -0.55 (-3.32, 2.18) | 0.29 (-0.61, 6.68) | 0.15 (-4.46, 4.71) | HC-MP | | |
| -10.09 (-14.66, -5.51) | -4.27 (-7.73, -0.54) | -5.01 (-9.95, 0.19) | -4.23 (-10.38, 2.01) | -3.93 (-8.89, 0.68) | -3.64 (-8.46, 1.32) | -3.15 (-7.78, 1.28) | -3.49 (-12.16, 5.13) | -3.11 (+8.89, 2.73) | -1.72 (-4.95, 1.46) | -2.09 (-6.03, 1.92) | -1.26 (-4.85, 2.43) | -0.98 (-3.36, 1.44) | -0.13 (-5.56, 5.34) | -0.28 (-3.51, 2.93) | -0.43 (-3.68, 2.90) | HC-SP | |
| -10.96 (-16.08, -5.92) | -5.14 (-9.71, -0.45) | -5.88 (-11.74, 0.11) | -5.09 (-12.04, 1.79) | -4.80 (-11.89, 1.81) | -4.51 (-7.88, -1.14) | -4.01 (-9.03, 0.67) | -4.38 (-13.62, 4.77) | -3.99 (-10.69, 2.67) | -2.59 (-6.96, 1.61) | -2.96 (-8.16, 2.22) | -2.13 (-7.33, 3.0) | -1.85 (-6.66, 2.85) | -0.99 (-8.39, 6.30) | -1.15 (-7.03, 4.60) | -1.30 (-5.84, 3.20) | -0.87 (-5.79, 3.93) | HC-MP-CR |
| Significant eff | fects are indica | ated in bold ter | ct. | | | | | | | | | | | | | | |

GRADE rating: very low; low; wery low; low; moderate; VL, very low; S, standard; CR, calorie restric GRADE rating: very low; low; low; moderate; high.

Table 3 Comparative effects of structured dietary programs on fasting plasma glucose (mmol/L) at 6-month

| VLC-HP-CR | | | | | | | | | | | | | | | | | |
|-------------------------------|---|-------------------------|-------------------------|------------------------|------------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|----------|
| -0.78 (-2.62, 0.99) | VLC-MP-CR | | | | | | | | | | | | | | | | |
| 1.15 (-1.05, 3.34) | 1.93 (+0.54, 4.44) | LC-MP -CR | | | | | | | | | | | | | | | |
| -0.51 (-2.78, 1.74) | 1.42 (+0.54, 3.39) | 0.64 (-0.95, 2.17) | LC-HP-CR | | | | | | | | | | | | | | |
| -0.97 (-3.52, 1.55) | -0.46 (-2.35, 1.44) | 0.19 (-1.81, 2.1) | 0.96 (-1.32, 3.26) | LC-HP | | | | | | | | | | | | | |
| -0.21 (-1.61, 1.2) | 0.56 (=1.24, 2.46) | -1.37 (-3.44, 0.76) | -0.86 (-2.29, 0.67) | -0.40 (-2.22, 1.50) | MC-HP | | | | | | | | | | | | |
| -0.28 (-1.36, 0.75) | 0.50 (+0.97, 1.96) | -1.44 (-3.46, 0.56) | -0.92 (-2.24, 0.38) | -0.46 (-2.23, 1.28) | -0.06 (-1.24, 1.01) | MC-MP-CR | | | | | | | | | | | |
| -0.37 (-1.59, 0.81) | 0.41 (=1.29, 2.13) | -1.52 (-3.52, 0.46) | -1.01 (-2.31, 0.28) | -0.55 (-2.27, 1.17) | -0.15 (-1.15, 0.76) | -0.09 (-0.95, 0.79) | MC-MP | | | | | | | | | | |
| -0.42 (-1.55, 0.73) | 0.35 (=1.24, 2.07) | -1.57 (-3.56, 0.47) | -1.07 (-2.12, 0.10) | -0.61 (-2.21, 1.1) | -0.21 (-1.26, 0.88) | -0.15 (-0.85, 0.69) | -0.05 (-0.8, 0.79) | MC-HP-CR | | | | | | | | | |
| -1.55 (-4.86, 1.76) | -1.03 (-3.97, 1.89) | -0.39 (-3.25, 2.43) | 0.39 (-2.61, 3.41) | -0.57 (-3.73, 2.57) | -0.18 (-3.05, 2.66) | -0.11 (-2.74, 2.53) | -0.02 (=2.78, 2.75) | 0.03 (-2.74, 2.75) | HC-SF-CR | | | | | | | | |
| -0.59 (-1.69, 0.46) | 0.19 (-1.70, 2.09) | -1.75 (-4.02, 0.51) | -1.23 (-2.89, 0.44) | -0.78 (-2.81, 1.26) | -0.38 (-1.91, 1.09) | -0.31 (-1.51, 0.91) | -0.22 (-1.5, 1.06) | -0.17 (-1.5, 1.08) | -0.20 (-3.10, 2.70) | Routine care | | | | | | | |
| -0.72 (-2.21, 0.66) | 0.06 (-1.84, 1.89) | -1.88 (-4.08, 0.25) | -1.36 (-2.49, -0.31) | -0.91 (-2.66, 0.78) | -0.50 (-1.9, 0.73) | -0.44 (-1.61, 0.68) | -0.35 (-1.49, 0.71) | -0.3 (-1.35, 0.59) | -0.34 (-3.21, 2.51) | -0.13 (-1.7, 1.37) | MC-SP | | | | | | |
| -0.84 (-2.31, 0.65) | -0.06 (-1.91, 1.89) | -1.99 (-4.17, 0.23) | -1.48 (-2.86, -0.01) | -1.02 (-2.77, 0.8) | -0.63 (-1.99, 0.76) | -0.56 (-1.72, 0.71) | -0.47 (-1.61, 0.75) | -0.41 (-1.44, 0.59) | -0.44 (-3.31, 2.47) | -0.25 (-1.8, 1.37) | -0.12 (-1.27, 1.19) | MC-SP-CR | | | | | |
| -2.0 (-4.03, 0.02) | -1.49 (-2.62, -0.36) | -0.84 (-2.10, 0.36) | -0.07 (-1.77, 1.65) | -1.03 (-2.55, 0.49) | -0.63 (-1.74, 0.39) | -0.57 (-1.43, 0.32) | -0.47 (-1.28, 0.32) | -0.42 (-1.11, 0.16) | -0.45 (-3.23, 2.31) | -0.25 (-1.6, 1.09) | -0.12 (-0.89, 0.72) | 0 (+0.98, 0.89) | HC-SP | | | | |
| -2.20 (-4.08, -0.32) | -1.69 (-2.94, -0.41) | -1.05 (-2.2, 0.07) | -0.27 (-1.88, 1.38) | -1.23 (-2.92, 0.48) | -0.83 (-1.8, 0.08) | -0.77 (-1.46, -0.04) | -0.68 (-1.34, 0) | -0.62 (-1.39, 0.05) | -0.66 (-3.38, 2.06) | -0.45 (-1.72, 0.81) | -0.33 (-1.35, 0.79) | -0.21 (-1.39, 0.9) | -0.20 (-0.95, 0.56) | HC-MP | | | |
| -2.35 (-4.52, -0.14) | -1.84 (-3.30, -0.29) | -1.19 (-2.66, 0.29) | -0.42 (-2.27, 1.54) | -1.38 (-3.25, 0.58) | -0.98 (-2.33, 0.37) | -0.92 (-2.08, 0.35) | -0.83 (-1.83, 0.26) | -0.77 (-1.85, 0.28) | -0.80 (-3.68, 2.11) | -0.60 (-2.13, 0.99) | -0.48 (-1.77, 0.97) | -0.36 (-1.78, 1.06) | -0.35 (-1.46, 0.84) | -0.15 (-1.25, 1.01) | HC-HP | | |
| -2.67 (-5.0, -0.36) | -2.15 (-3.91, -0.39) | -1.51 (-2.99, -0.09) | -0.73 (-2.66, 1.20) | -1.70 (-3.81, 0.41) | -1.29 (-2.96, 0.28) | -1.23 (-2.48, 0.03) | -1.14 (-2.59, 0.29) | -1.09 (-2.55, 0.27) | -1.12 (-4.02, 1.79) | -0.92 (-2.26, 0.41) | -0.79 (-2.41, 0.88) | -0.67 (-2.41, 0.98) | -0.66 (-2.14, 0.79) | -0.46 (-1.86, 0.9) | -0.31 (+2.04, 1.32) | HC-MP-CR | |
| -2.88 (-5.3, -0.37) | -2.37 (-4.12, -0.51) | -1.73 (-3.52, 0.12) | -0.95 (-3.07, 1.30) | -1.91 (-4.04, 0.32) | -1.51 (-3.28, 0.29) | -1.45 (-3.0, 0.24) | -1.36 (-2.94, 0.33) | -1.30 (-2.73, 0.12) | -1.33 (-4.38, 1.78) | -1.14 (-3.01, 0.84) | -1.01 (-2.64. 0.82) | -0.89 (-2.62, 0.88) | -0.89 (-2.39, 0.74) | -0.68 (-2.23, 0.97) | -0.53 (-2.29, 1.26) | -0.22 (-2.16, 1.85) | HC-SP-CR |
| Significant of Abbreviatio | Significant fields are indicated in bold text. Abbreviations: C, carbohydrate; P, protein; H, high; L, low; A, moderate; VL, very low; S, standard; CR, calorie restricted | | | | | | | | | | | | | | | | |

-1.36 mmol/L, 95%CrI: -2.49 to -0.31; GRADE = moderate) and moderate carbohydrate, standard protein, calorie-restricted diet (mean difference: -1.48 mmol/L, 95%CrI: -2.86 to -0.01; GRADE = moderate).

At 12-month (Additional file 1: Table S8), the results suggested evidence of moderate certainty that very low carbohydrate, high protein, calorie-restricted diet was effective in reducing FPG when compared with moderate carbohydrate, moderate protein diet (mean difference: - 1.21 mmol/L, 95%CrI: - 2.39 to - 0.04) and high carbohydrate, moderate protein diet (mean difference: - 1.27 mmol/L, 95%CrI - 2.31 to - 0.20). Other dietary programs were not effective at 12-month follow-up in reducing FPG.

Comparative effects of different structured dietary compositions on LDL cholesterol at 6-month are indicated in Table 4. There was evidence that low carbohydrate, high protein, calorie-restricted diet was effective in

| Table 4 Comparativ | e effects of structured | dietary programs on | low-density lipoprotein | cholesterol (mmol/L) at 6-month |
|--------------------|-------------------------|---------------------|-------------------------|---------------------------------|
|--------------------|-------------------------|---------------------|-------------------------|---------------------------------|

| -0.34 (-0.76, 0.09) | -0.27 (-0.56, 0.03) | -0.22 (-0.51, 0.07) | -0.15 (-0.35, 0.06) | -0.04 (-0.17, 0.1) | MC-HP-CR | | | | | | | | | | |
|-------------------------|-------------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|-------------------|----------|----------|
| -0.37 (-0.86, 0.15) | -0.3 (-0.63, 0.05) | -0.26 (-0.64, 0.16) | -0.18 (-0.5, 0.18) | -0.07 (-0.36, 0.25) | -0.03 (-0.29, 0.25) | MC-HP | | | | | | | | | |
| -0.42 (-0.91, 0.09) | -0.36 (-0.7, 0.02) | -0.31 (-0.69, 0.1) | -0.24 (-0.55, 0.12) | -0.13 (-0.41, 0.19) | -0.09 (-0.34, 0.19) | -0.06 (-0.39, 0.29) | MC-MP | | | | | | | | |
| -0.43 (-0.89, 0.07) | -0.37 (-0.65, -0.03) | -0.32 (-0.66, 0.08) | -0.24 (-0.51, 0.09) | -0.14 (-0.36, 0.16) | -0.1 (-0.29, 0.16) | -0.06 (-0.35, 0.25) | -0.01 (-0.25, 0.25) | VLC-MP-CR | | | | | | | |
| -0.45 (-0.95, 0.08) | -0.38 (-0.74, 0) | -0.34 (-0.74, 0.09) | -0.26 (-0.6, 0.11) | -0.15 (-0.46, 0.18) | -0.11 (-0.39, 0.19) | -0.08 (-0.43, 0.27) | -0.02 (-0.38, 0.32) | -0.02 (-0.33, 0.28) | VLC-HP-CR | | | | | | |
| -0.46 (-0.96, 0.04) | -0.39 (-0.78, -0.02) | -0.35 (-0.74, 0.03) | -0.27 (-0.6, 0.05) | -0.16 (-0.46, 0.12) | -0.12 (-0.39, 0.12) | -0.09 (-0.48, 0.25) | -0.03 (-0.42, 0.31) | -0.03 (-0.4, 0.27) | -0.01 (-0.41, 0.35) | HC-SP-CR | | | | | |
| -0.47 (-0.97, 0.04) | -0.41 (-0.77, -0.02) | -0.36 (-0.75, 0.04) | -0.28 (-0.61, 0.07) | -0.17 (-0.47, 0.13) | -0.13 (-0.4, 0.14) | -0.1 (-0.46, 0.25) | -0.04 (-0.26, 0.13) | -0.04 (-0.34, 0.22) | -0.02 (-0.39, 0.34) | -0.01 (-0.37, 0.37) | HC-HP | | | | |
| -0.48 (-0.99, 0.05) | -0.41 (-0.77, -0.04) | -0.37 (-0.77, 0.05) | -0.29 (-0.64, 0.08) | -0.18 (-0.5, 0.15) | -0.14 (-0.43, 0.16) | -0.11 (-0.47, 0.24) | -0.05 (-0.42, 0.3) | -0.05 (-0.38, 0.25) | -0.03 (-0.21, 0.14) | -0.02 (-0.39, 0.37) | -0.01 (-0.38, 0.36) | Routine Care | | | |
| -0.49 (-0.94, -0.03) | -0.43 (-0.7, -0.14) | -0.38 (-0.7, -0.04) | -0.3 (-0.54, -0.04) | -0.2 (-0.38, 0.02) | -0.16 (-0.3, 0) | -0.12 (-0.36, 0.1) | -0.07 (-0.33, 0.18) | -0.06 (-0.28, 0.12) | -0.04 (-0.32, 0.22) | -0.03 (-0.31, 0.27) | -0.02 (-0.29, 0.26) | -0.01 (-0.29, 0.27) | HC-MP | | |
| -0.49 (-0.93, -0.03) | -0.43 (-0.68, -0.15) | -0.38 (-0.69, -0.04) | -0.3 (-0.54, -0.04) | -0.2 (-0.38, 0.02) | -0.16 (-0.29, 0) | -0.12 (-0.38, 0.12) | -0.07 (-0.32, 0.18) | -0.05 (-0.26, 0.1) | -0.04 (-0.29, 0.2) | -0.03 (-0.3, 0.27) | -0.02 (-0.29, 0.25) | -0.01 (-0.27, 0.25) | 0 (-0.11, 0.1) | MC-MP-CR | |
| -0.59 | -0.52 | -0.48 | -0.4 | -0.29 | -0.25 | -0.22 | -0.16 | -0.16 | -0.14 | -0.13 | -0.12 | -0.11 | -0.1 | -0.1 | LC-MP-CR |

Abbreviations: C, carbohydrate; P, protein; H, high; L, low; M, moderate; VL, very low; S, standard; CR, calorie restricte GRADE rating: very low; low; moderate; high.

reducing LDL when compared with high carbohydrate, moderate protein diet (mean difference: -0.49 mmol/L, 95%CrI: -0.94 to -0.03; GRADE=moderate) and low carbohydrate, moderate protein, calorie-restricted diet (mean difference: -0.59 mmol/L, 95%CrI: -1.06 to -0.09; GRADE=moderate). Moderate carbohydrate, standard protein, calorie-restricted diet was also effective in reducing LDL when compared with high carbohydrate, moderate protein diet (mean difference: -0.38 mmol/L, 95%CrI: -0.7 to -0.04; GRADE=moderate) and low carbohydrate, moderate protein, calorie-restricted diet (mean difference: -0.48 mmol/L, 95%CrI: -0.84 to -0.09; GRADE=moderate).

At 12-month (Additional file 1: Table S9), the results suggested evidence of moderate certainty that a moderate carbohydrate, standard protein, calorie restricted diet was effective in reducing LDL when compared with very low carbohydrate, high protein, calorie restricted diet (mean difference: -0.87 mmol/L, 95%CrI: -1.55 to - 0.16). Low carbohydrate, moderate protein, calorie-restricted diet was also effective in reducing LDL when compared with very low carbohydrate, high protein, calorie-restricted diet (mean difference: -0.79 mmol/L, 95%CrI: -1.54 to - 0.04; GRADE = moderate).

Treatment ranking

At 6-month (Table 5), very low carbohydrate, high protein, calorie-restricted diets were ranked best in reducing HbA1c, followed by low carbohydrate, moderate protein, calorie-restricted diet. In reducing weight, very low carbohydrate, high protein, calorie-restricted diets were ranked best, followed by low carbohydrate, high protein, calorie-restricted diet. In reducing FPG, very low carbohydrate, high protein, calorie-restricted diets and very low carbohydrate, moderate protein, calorie-restricted diets were ranked best, followed by low carbohydrate, moderate protein, calorie-restricted diets. In reducing LDL, low carbohydrate, high protein, calorie-restricted diets and high carbohydrate, moderate protein, calorierestricted diets were ranked best, followed by moderate carbohydrate, standard protein, calorie calorie-restricted diets.

At 12-month (Table 6), very low carbohydrate, high protein, calorie-restricted diets were ranked best in reducing HbA1c and FPG, followed by low carbohydrate, high protein diets. In reducing weight, low carbohydrate, high protein diets were ranked best, followed by very low carbohydrate, high protein, calorie-restricted diets. In reducing LDL, moderate carbohydrate, standard protein, calorie-restricted diets were ranked best, followed by low carbohydrate, high protein, calorie-restricted diets.

Subgroup and sensitivity analyses

We planned to perform two pre-specified sensitivity analyses to compare the effects of different dietary compositions on primary and secondary outcomes in patients with type 2 diabetes and overweight or obesity and trials with a low risk of bias. However, due to network constraints (disconnected network), we could not perform subgroup analyses in patients with

Table 5 Treatment ranking according to SUCRA values (%) at 6-month follow-up

| Dietary programs | HbA _{1c} | Weight | FPG | LDL |
|--|-------------------|--------|-----|-----|
| Very low carbohydrate-High protein diet (Calorie restricted) | 95 | 99 | 92 | 37 |
| Low carbohydrate-Moderate protein diet (Calorie restricted) | 80 | 72 | 91 | 10 |
| Low carbohydrate-High protein diet (Calorie restricted) | 76 | 77 | 89 | 90 |
| Very low carbohydrate-Moderate protein diet | 76 | 58 | - | - |
| Very low carbohydrate-High protein diet | 74 | 58 | - | - |
| Very low carbohydrate-Moderate protein diet (Calorie restricted) | 65 | 65 | 92 | 41 |
| Moderate carbohydrate-Moderate protein diet | 60 | 44 | 59 | 42 |
| Moderate carbohydrate-High protein diet (Calorie restricted) | 48 | 33 | 57 | 59 |
| High carbohydrate-High protein diet | 44 | 36 | 22 | 25 |
| Moderate carbohydrate-Standard protein diet (Calorie restricted) | 43 | 28 | 36 | 86 |
| Moderate carbohydrate-Moderate protein diet (Calorie restricted) | 41 | 48 | 63 | 25 |
| Moderate carbohydrate-Standard protein diet | 40 | 26 | 41 | 80 |
| Routine Care | 36 | 61 | 47 | 31 |
| Moderate carbohydrate-High protein diet | 33 | 68 | 65 | 53 |
| High carbohydrate-Moderate protein diet | 30 | 24 | 25 | 25 |
| High carbohydrate-Standard protein diet | 28 | 20 | 34 | 65 |
| High carbohydrate-Moderate protein diet (Calorie restricted) | 18 | 15 | 15 | 90 |
| High carbohydrate-Standard protein diet (Calorie restricted) | 13 | - | 12 | 34 |
| Low carbohydrate-High protein diet | - | 66 | 74 | - |
| High carbohydrate-Standard protein diet (Calorie restricted) | - | - | 53 | - |

SUCRA surface under the cumulative ranking curve, FPG fasting plasma glucose, LDL low-density lipoprotein cholesterol

Table 6 Treatment ranking according to SUCRA values (%) at 12-month follow-up

| Dietary programs | HbA _{1c} | Weight | FPG | LDL |
|--|-------------------|--------|-----|-----|
| Very low carbohydrate-High protein diet (Calorie restricted) | 93 | 73 | 91 | 15 |
| Low carbohydrate-High protein diet | 72 | 99 | 71 | 32 |
| Moderate carbohydrate-Standard protein diet (Calorie restricted) | 70 | 57 | 69 | 86 |
| Moderate carbohydrate-Moderate protein diet (Calorie restricted) | 58 | 49 | 56 | 68 |
| Moderate carbohydrate-Moderate protein diet | 50 | 63 | 49 | 20 |
| Low carbohydrate-High protein diet (Calorie restricted) | 49 | 32 | 48 | 75 |
| High carbohydrate-Moderate protein diet | 47 | 50 | 47 | 20 |
| High carbohydrate-Standard protein diet | 43 | - | 43 | - |
| Moderate carbohydrate-High protein diet | 42 | 57 | 41 | 16 |
| Moderate carbohydrate-High protein diet (Calorie restricted) | 41 | 37 | 40 | 52 |
| High carbohydrate-Moderate protein diet (Calorie restricted) | 36 | 11 | 35 | 69 |
| Low carbohydrate-Moderate protein diet (Calorie restricted) | 32 | 23 | 31 | 73 |
| High carbohydrate-Standard protein diet (Calorie restricted) | 16 | _ | 15 | 72 |

SUCRA surface under the cumulative ranking curve, FPG fasting plasma glucose, LDL low-density lipoprotein cholesterol

overweight or obesity. The only exception was body weight at 6-month follow-up, for which we conducted a sensitivity analysis in patients with overweight or obesity (Additional file 1: Table S10). The results showed that very low carbohydrate, high protein, calorierestricted diet followed by very low carbohydrate, moderate protein, calorie-restricted diet was most effective in reducing body weight when compared with other dietary programs (range of mean difference: -5.65 kg to -10.46 kg) (range of mean difference: -3.96 kg to -6.25 kg), respectively.

In addition, due to the limited number of trials with a low risk of bias, as assessed by version 2.0 of the Cochrane risk of bias tool, we did not perform subgroup analyses by risk of bias. The GRADE evidence rating for direct, indirect, and network estimates are presented in Additional file 1: Tables S11–S18. In brief, the certainty of the evidence was rated moderate for the effects of very low carbohydrate, high protein, calorie-restricted diet; low carbohydrate, moderate protein, calorie-restricted diet and low carbohydrate, high protein, calorie-restricted diet in reducing HbA_{1c} at 6-month follow-up. Of note, the magnitude of the effects was larger than the MCID threshold for HbA_{1c} (0.5%) for the effects of these diets against other dietary compositions. At 12-month, the certainty of the evidence was rated moderate only for the effects of very low carbohydrate, high protein, calorie-restricted diet in reducing HbA_{1c} with moderate effect sizes.

In reducing weight at 6-month follow-up, the certainty of evidence was rated moderate for the effects of very low carbohydrate, high protein, calorie-restricted diet; low carbohydrate, high protein, calorie-restricted diet; low carbohydrate, moderate protein, calorie-restricted diet and very low carbohydrate, moderate protein, calorierestricted diet. The effect sizes were moderate or small but important for very low carbohydrate, high protein, calorie-restricted diet and for the other three above-mentioned diets, the effect sizes were small but important. At 12-month follow-up, the certainty of the evidence was rated moderate only for the effects of low carbohydrate, high protein diet in reducing weight with moderate effect sizes.

In reducing FPG at 6-month follow-up, the certainty of evidence was rated moderate for the effects of very low carbohydrate, high protein, calorie-restricted diet; very low carbohydrate, moderate protein, calorie-restricted diet; low carbohydrate, moderate protein, calorierestricted diet and low carbohydrate, high protein, calorie-restricted diet. At 12-month follow-up, the certainty of the evidence was rated moderate only for the effects of very low carbohydrate, high protein, calorie-restricted diet in reducing FPG. The magnitude of the effects was larger than the MCID threshold for FPG (1.60 mmol/L) for the effects of these diets against other dietary compositions at both 6 and 12-month follow-up.

In reducing LDL at 6-month follow-up, the certainty of evidence was rated moderate for the effects of low carbohydrate, high protein, calorie-restricted diet and moderate carbohydrate, standard protein, calorierestricted diet. The effect sizes were large or moderate for low carbohydrate, high protein, calorie-restricted diet and for moderate carbohydrate, standard protein, calorie-restricted diet the effect sizes were moderate. At 12-month follow-up, the certainty of evidence was rated moderate for the effects of moderate carbohydrate, standard protein, calorie-restricted diet and low carbohydrate, moderate protein, calorie-restricted diet in reducing LDL with a large effect size.

Discussion

Principal findings

The present systematic review and network meta-analysis of RCTs assess and rank the comparative effects of different macronutrient compositions for type 2 diabetes management. According to our findings, obtained from 80 controlled trials, very low carbohydrate, high protein, calorie-restricted diet was the most effective in reducing HbA_{1c} and FPG at both 6- and 12-month follow-ups with moderate certainty of evidence, and the effect size was moderate for HbA_{1c} and small but important for FPG. Similarly, in reducing weight at 6-month follow-up, the results suggested evidence of moderate certainty that a very low carbohydrate, high protein, calorie-restricted diet was most effective by moderate or small but important effect size. But at 12-month follow-up with moderate certainty of the evidence, low carbohydrate, high protein diet was the most effective in reducing weight by moderate effect size. In reducing LDL our findings showed that low carbohydrate, high protein, calorie-restricted diet was ranked best with moderate certainty of evidence at 6-month follow-up that the magnitude of the effects was moderate or large. At 12-month follow-up, a moderate carbohydrate, standard protein, calorie-restricted diet with moderate certainty of evidence was most effective in reducing LDL with a large effect size.

Overall, our results suggest with moderate certainty of evidence that a very low-carbohydrate, high-protein, calorie-restricted diet was the most effective dietary composition in improving most of our primary and secondary outcomes.

Comparison with other studies

The results of a recent meta-analysis of randomized trials showed that every 500 kcal per day reduction in total energy intake at 6 months follow-up, resulted in a significant reduction in body weight and HbA1c, but these effects were significantly reduced at 12 months [117]. The results of our study are also consistent with the mentioned study, so that the most effective dietary composition to improve all our outcomes included calorie restriction except weight at 12 months follow-up which can point to the importance of calorie reduction in diabetes management. Another study on calorie restriction showed that restricting energy intake to 900 kcal per day resulted in significant reductions in muscle mass, suggesting that less restrictive interventions may be preferable [12]. This study only assessed the calorie restriction status in the management of diabetes. A network metaanalysis suggested that caloric restriction was ranked as the best dietary pattern for reducing weight and waist circumference. Low-carbohydrate diets were best in improving body mass index and high-density lipoprotein cholesterol. Low-glycemic-index diets were ranked as the best pattern in reducing total cholesterol and low-density lipoprotein [11]. In the above study, unlike our study, the focus is not on the composition of the diet, i.e. the percentage of macronutrients, but rather on examining different food patterns, apart from paying attention to the distribution of carbohydrates, proteins, and fats in the diet. Reporting the results of our study is more practical and transparent for use in patients with type 2 diabetes because it clearly explains how to distribute macronutrients to achieve diabetes control goals, and we also examined long-term effects in addition to short-term. The evidence of the reported results was of moderate to low quality in the mentioned study, and only 38.2% of the evidence found had minimal clinically important differences, which was a limitation of the study [11].

Network meta-analysis of forty-two randomized trials indicated that for glycemic control in patients with type 2 diabetes, the ketogenic diet, Mediterranean diet, moderate-carbohydrate diet, and low glycemic index diet were effective options [13]. In this study, the aim was not to find the best and most effective way to distribute macronutrients in the management of diabetes, because it examined dietary patterns, and in conditions such as a low-carbohydrate diet, only the percentage of carbohydrates in the diet was considered and the distribution of other macronutrients, which can be very useful in diet therapy, has not been investigated. Also, in the mentioned study, only glycemic control was examined as an outcome, and no comparison was made for different follow-up periods [13]. Another network meta-analysis also showed that the most effective dietary intervention for improving blood glucose was following the Mediterranean diet, and a low-carbohydrate diet was the best approach for improving anthropometric indices in patients with type 2 diabetes [14]. Two recent studies have shown that plant-based diets can improve insulin sensitivity and are beneficially associated with cardiovascular health and type 2 diabetes management [118, 119]. In the mentioned studies, despite our study, macronutrient composition was not evaluated and only dietary patterns were examined in the management of type 2 diabetes. The results of a dose-response meta-analysis showed that for every 10% reduction in the portion of carbohydrates in the energy intake, it is possible to reduce body weight, FPG, and HbA_{1c} in patients with type 2 diabetes. However, these observed effects weakened or disappeared at follow-up beyond 6 months [8]. These results are almost consistent with those obtained from our study, as we showed that a very low-carbohydrate, high-protein, and calorie-restricted diet had the greatest effect on reducing HbA_{1c}, weight, and FPG at the 6-month followup, but at the 12-month follow-up, the effect remained only for HbA_{1c} and FPG. Also, in the mentioned study, the results indicated a U-shaped effect for total cholesterol and LDL cholesterol at 6 months follow-up, with the greatest reduction at 40% carbohydrate [8]. In our study, the best dietary approach to reduce LDL in the 6-month follow-up was low carbohydrate, and in the 12-month follow-up, was moderate carbohydrate, which shows that severe carbohydrate restriction is not beneficial for improving LDL. Despite the results of the mentioned research and our study, A recent meta-analysis found that the ketogenic diet, which is associated with severe carbohydrate restriction, may improve lipid profiles but does not provide additional benefits for glycemic control or weight loss for patients with type 2 diabetes [10].

A meta-analysis of 23 clinical trials found that at sixmonth follow-up, low carbohydrate diets achieved higher diabetes remission rates when remission was defined as HbA1c < 6.5%. Also, low carbohydrate diets led to weight loss, reduced need for medication, and improved triglyceride levels at six months, but most of the benefits were lost at 12-month follow-up [34]. In our study, the results showed that restriction of carbohydrates to the range of less than 10% can have the greatest effect on reducing HbA_{1c}, weight, and FPG at the 6-month follow-up, but at the 12-month follow-up, the effect remained only for HbA_{1c} and FPG. For weight loss in the 12-month followup, restriction of carbohydrates to the range of 11–26% was probably the most effective approach due to the long-term acceptance of this diet by participants. The noteworthy point in our study is that not only the amount of carbohydrates in the diet was taken into account, but the high amount of protein intake was emphasized in both 6 and 12-month follow-ups to improve the study outcomes.

Clinical and public health implications

Despite the agreement on nutritional recommendations provided by scientific institutions [2, 5–7], there is still uncertainty and disagreement about the specific optimal ratio of carbohydrate, fat, and protein intake that will be effective for managing diabetes in most people. Also, so far, no meta-analysis has been conducted to examine the diet composition in detail, taking into account the percentage of macronutrients and the state of calorie restriction for the management of diabetes. In this study, in addition to addressing the optimal percentage of macronutrients and calorie status, we investigated the effectiveness of different dietary compositions in the short and long term in two periods at 6 and 12 months follow-up. Our findings suggested that a very low carbohydrate, high protein, calorie-restricted diet can be an effective dietary composition in the management of diabetes, but milder carbohydrate dietary restrictions are needed for longterm weight loss as well as lipid profile improvement. Since it is difficult for people with diabetes to adhere to very low carbohydrate diets in the long term, other diets can be recommended to patients, which after the very low carbohydrate, high protein, calorie-restricted diet had the greatest effect in our study. Such as low carbohydrate, high protein, calorie-restricted diet as well as a low-carbohydrate, moderate-protein, calorie-restricted diet was effective in further improving the outcomes of our study. Also, looking at the results, we find that increasing the proportion of dietary protein is an important component to more effectively modify diabetes-related outcomes, as other studies have shown that consuming higher levels of protein (20-30%) may increase satiety and as a result, it helps to manage diabetes.

Strengths and limitations

Our study has some strengths. First, our research was the network meta-analysis that included a large number of randomized trials on different macronutrient compositions for type 2 diabetes management and we analyzed the trials according to a predefined approach established based on our publicly available study protocol [17]. Second, we examined dietary composition in terms of the precise distribution of macronutrients with or without caloric restriction rather than assessing different predefined dietary patterns. This approach can be more practical and accurate for diet therapy in diabetes management. Third, to examine the long-term effects of dietary composition on diabetes-related outcomes, we made comparisons at 6- and 12-month follow-up periods, whereas other studies have not made such temporal comparisons. Fourth, we rated the certainty of evidence using the emerging GRADE approach and used MCID thresholds that were set for use in patients with type 2 diabetes, to rank dietary compositions from the most to the least effective.

Our meta-analysis had some limitations. First, the number of studies with long-term follow-up for diabeticrelated outcome control in patients with type 2 diabetes is limited. Second, We planned to perform sensitivity analyses to compare the effects of different dietary compositions on primary and secondary outcomes in patients with type 2 diabetes and overweight or obesity. However, due to limited studies and network constraints, we could not perform subgroup analyses in patients with overweight or obesity. Third, due to the nature of the studies in the field of dietary therapy and dietary composition, where the possibility of blinding and concealment is limited, the risk of bias in these clinical trials increases.

Future directions

In the future, more clinical trial studies with dietary interventions in different exact dietary compositions and calorie status should be conducted with longer follow-up periods to investigate the effects.

Conclusion

Our findings provide moderate-certainty evidence that a very low carbohydrate, high protein, calorie-restricted diet can be an effective dietary composition in managing diabetes, but milder dietary carbohydrate restriction for weight loss in the long-term and improvement of lipid profiles is needed.

Abbreviations

- CR Calorie restricted
- LC Low carbohydrate
- VLC Very low carbohydrate MC Moderate carbohydrate
- HC High carbohydrate
- SP Standard protein
- MP Moderate protein
- HP High protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41043-025-00818-1.

Additional file 1.Table S1. Search strategy to find potentially relevant articles for inclusion in the meta-analysis of macronutrient compositions in patients with type 2 diabetes. Table S2. Lists of studies excluded via full-text assessment and reasons for exclusions. Table S3. Characteristics of the primary trials included in the meta-analysis. Table S4. Risk of bias of the trials included in the meta-analysis (parallel trials). Table S5. Risk of bias of the trials included in the meta-analysis (cross-over trials). Table S6. Comparative effects of structured dietary programs on HbA1c (%) at 12-month. Table S7. Comparative effects of structured dietary programs on body weight (kg) at 12-month. Table S8. Comparative effects of structured dietary programs on fasting plasma glucose (mmol/L) at 12-month. Table S9. Comparative effects of dietary programs on low-density lipoprotein cholesterol (mmol/L) at 12-month. Table S10 Comparative effects of dietary programs on body weight at 6-month in the subgroup of patients with type 2 diabetes and overweight or obesity. Table S11. GRADE evidence table for the effects of dietary programs on HbA1c at 6-month. Table S12. GRADE evidence table for the effects of dietary programs on HbA1c at 12-month. Table S13. GRADE evidence table for the effects of dietary programs on body weight (kg) at 6-month. Table S14. GRADE evidence table for the effects of dietary programs on body weight at 12-month. Table S15. GRADE evidence table for the effects of dietary programs on fasting plasma glucose (mmol/L) at 6-month. Table S16. GRADE evidence table for the effects of dietary programs on fasting plasma glucose (mmol/L) at 12-month. Table S17. GRADE evidence table for the effects of dietary programs on low-density lipoprotein cholesterol (mmol/L) at 6-month. Table S18. GRADE evidence table for the effects of dietary programs on low-density lipoprotein cholesterol (mmol/L) at 12-month. Fig. S1. Distribution of mean age across the available direct comparisons. Fig. S2. Distribution of diabetes duration across the available direct comparisons. Fig. S3. Distribution of female participants across the available direct comparisons. Fig. S4. Distribution of baseline mean glycated hemoglobin concentration across the available direct comparisons. Fig. S5. Comparison-adjusted funnel plot involving all trials in the analysis of fasting plasma glucose at 6-month. Fig. S6. Comparison-adjusted funnel plot involving all trials in the analysis

of glycated hemoglobin at 6-month. Fig. S7. Comparison-adjusted funnel plot involving all trials in the analysis of low-density lipoprotein cholesterol at 6-month. Fig. S8. Comparison-adjusted funnel plot involving all trials in the analysis of body weight at 6-month. Fig. S9. Comparison-adjusted funnel plot involving all trials in the analysis of glycated hemoglobin at 12-month. Fig. S10. Comparison-adjusted funnel plot involving all trials in the analysis of low-density lipoprotein cholesterol at 12-month. Fig. S11. Comparison-adjusted funnel plot involving all trials in the analysis of body weight at 12-month. Fig. S12. Comparison-adjusted funnel plot involving all trials in the analysis of fasting plasma glucose at 12-month. Fig. S13. Literature search and study selection process. Fig. S14. Network diagram showing the comparative effects of different dietary compositions on fasting plasma glucose at 6-month. Fig. S15. Network diagram showing the comparative effects of different dietary compositions on low-density lipoprotein cholesterol at 6-month. Fig. S16. Network diagram showing the comparative effects of different dietary compositions on body weight at 6-month. Fig. S17. Network diagram showing the comparative effects of different dietary compositions on low-density lipoprotein cholesterol at 12-month. Fig. S18. Network diagram showing the comparative effects of different dietary compositions on body weight at 12-month. Fig. S19. Network diagram showing the comparative effects of different dietary compositions on fasting plasma glucose at 12-month.

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Author contributions

A.J. and S.SB. conceived and designed the study; N.B. and A.J. conducted systematic search, screened articles, and selected eligible articles; N.B. and A.J. extracted the information from eligible studies and performed quality assessments; A.J. and S.SB. performed analyses and interpreted the results; N.B. and A.J. wrote the first draft of the manuscript; S.SB. critically revised the manuscript. S.SB. is the guarantor. All authors have read and approved the final manuscript.

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No datasets were generated or analysed during the current study.

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The authors declare no competing interests.

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