Original Article

Effect of dietary carbohydrate intake on glycaemic control and insulin resistance in type 2 diabetes: A systematic review and meta-analysis

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Background and Objectives: The aim of this study was to elucidate the dose-response relationship between dietary carbohydrate consumption and the improvement of glycemic control and insulin sensitivity in individuals with type 2 diabetes mellitus (T2DM), following an intensive dietary intervention. **Methods and Study Design:** Randomized controlled trials published up to December 2023 were systematically reviewed from four databases: PubMed, Embase, Web of Science, and Cochrane Database of Systematic Reviews. Primary outcomes included: glycated hemoglobin (HbA1c), fasting glucose (FG); and secondary outcomes included: BMI, fasting insulin (FI), Homeostasis Model Assessment−Insulin Resistance (HOMA−IR). We performed a random−effects dose−response meta−analysis to estimate mean differences (MDs) for each 10% reduction in carbohydrate intake. **Results:** A total of 38 articles were analyzed, encompassing 2,831 total participants. Compared to the highest recorded carbohydrate intake (65%), reducing carbohydrate intake to 5% showed that for every 10% decrease, the following improvements were observed: HbA1c (MD: 0.39%; 95%CI: -0.5 to -0.28%), FG (MD: 0.55 mmol/L; 95%CI: -0.82 to -0.28 mmol/L), BMI (MD: -0.83 kg/m^2; 95%CI: -1.27 to -0.38 kg/m^2), FI (MD: -2.19 pmol/L; 95%CI: -3.64 to -0.73 pmol/L), HOMA-IR (MD: -1.53; 95%CI: -3.09 to 0.03). **Conclusions:** Reducing dietary carbohydrate intake significantly improves glycemic control and insulin resistance in individuals with type 2 diabetes. A linear reduction in carbohydrate intake was observed, with significant effects occurring within the first 6 months of the intervention. However, these effects diminished beyond this period. Notably, the improvements in glycemic parameters were not significantly affected by whether calorie restriction was implemented.

Key Words: type 2 diabetes, diet carbohydrate intake, carbohydrate restriction, randomized controlled trial, meta-analysis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is fundamentally characterized by the dysfunction of pancreatic β-cell, leading to insufficient insulin secretion that cannot effectively counteract the prevailing insulin resistance.[1] Recent studies have indicated that a reduction in glucose intake mitigates glucose toxicity and enhances glycemic control.[2] Careful management of the glycemic response to dietary carbohydrates is crucial for improving postprandial glucose levels and optimizing overall glycemic control in individuals with T2DM.

Traditionally, diabetes management guidelines have recommended a carbohydrate intake of 45% to 60% of total calories. However, recent reviews highlight the effectiveness of various carbohydrate-restricted diets in managing T2DM. This spectrum includes moderate carbohydrate diets (26-45% of total calories or approximately 130-230 g daily), low-carbohydrate diets (10-26% of total calories or 50-130 g daily), and ketogenic diets, defined by an intake of ≤10% of total calories (20-50 g daily). Multiple systematic reviews and meta-analyses of interventional studies provide evidence supporting the short-term benefits of reduced carbohydrate diets on glycemic control in T2DM.[3-5] However, these studies primarily rely on simple pairwise comparisons, which are insufficient to identify the optimal carbohydrate intake for dietary intervention.

Conducting a dose-response meta-analysis to assess mean differences is a valuable methodology for identifying the most effective dosage for implementing therapeutic interventions.[6] Hence, the present study aimed to investigate the potential relationship between dietary carbohydrate intake and glycemic control in individuals with T2DM. This objective was pursued through a rigorous dose-response meta-analysis of randomized controlled trials (RCTs), encompassing a wide range of carbohydrate intake in T2DM patients, from 5% to 65% of total caloric intake.

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METHODS

The present systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy

The protocol for this systematic review was registered in advance and is publicly accessible(PROSPERO CRD42023493156). Utilizing PubMed, Embase, Web of Science, and the Cochrane Database of Systematic Reviews, a comprehensive literature search was performed in December 2023. The search strategy encompassed key terms such as "Carbohydrate intake", "Type 2 Diabetes Mellitus", and "randomized controlled trial". The complete list of search terms is detailed in Supplementary Table 1.

Selection criteria

The inclusion criteria were as follow: 1) randomized trials with either a parallel or crossover design, conducted among adults (≥18 years) with type 2 diabetes; 2) trials assessing the impact of a diet comprising no more than 45% of total caloric intake from carbohydrates, with or without additional interventions such as calorie restriction, physical activity, and behavioral support, compared to a control diet; 3) trials that reported the quantity of dietary carbohydrate intake, expressed as a percentage of total energy intake or in grams per day, for both the intervention and control groups.

Exclusion criteria

Exclusion criteria were as follow: 1) study subjects that follow an alternative dietary treatment or medical nutrition; 2) non-English studies, animal and cell culture studies.

Outcomes

In the context of this systematic review, we prioritized changes in fasting glucose (FG) and HbA1c as the primary outcome. Secondary outcomes included changes in BMI, fasting insulin (FI) and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR).

Two investigators (JY.L, XK.Z) independently conducted the literature search, performed initial screenings of titles and abstracts from the retrieved articles, reviewed full texts thoroughly, and determined the eligibility of articles for inclusion in the meta-analysis. Any discrepancies were resolved through discussion or by consulting a third investigator if necessary.

Data extraction

Two reviewers, JY.L and M.C., independently evaluated the risk of bias in the included studies using established assessment criteria. They also extracted outcome data based on mean differences from baseline changes across all trials. In cases where discrepancies arose due to different measurement methods, the reviewers proactively standardized the results onto a consistent scale to ensure comparability for the dose-response meta-analysis. Any non-standard units were converted to their conventional equivalents to facilitate accurate analysis and interpretation. Discrepancies between reviewers were resolved through discussion or by consulting a third reviewer if consensus could not be reached.

Quality assessment

The risk of bias for the primary outcome was meticulously evaluated following the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The methodological quality of the studies was rigorously assessed across seven domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias. Criteria used for low risk, high risk, and unclear risk were those described in the Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis and analysis

In this systematic review, we utilized mean differences and their respective 95% confidence intervals (CIs) as metrics for effect size to reflect changes in both primary and secondary outcomes across the included studies.

For each study group, the change from baseline was determined. When the mean values and standard deviations (SDs) of these changes were not directly reported in the text or figures, we applied the methodologies detailed in the Cochrane Handbook[7] to estimate these parameters from pre- and post-intervention measurements. In cases where only standard errors (SEs) were provided in lieu of SDs, we converted SEs to SDs following the guidance provided by the same handbook.[7] When neither SD nor SE were available from the trials, we approximated the average SD by leveraging data from other trials within the meta-analysis.[8] For trials presenting median data rather than means, we standardized the methods to equivalent mean values using established statistical methods, ensuring uniformity and comparability across all included studies.[9,10]

We systematically computed the mean differences in outcomes, along with their corresponding SEs, between the intervention and control groups for each 10% reduction in carbohydrate calorie intake within individual trials. This calculation ranged from the maximum reported carbohydrate intake to a minimal intake of 5%, normalized against a benchmark of 65% carbohydrate intake. For these computations, we utilized the methodology developed by Crippa and Orsini.[6] The calculations required several key data points from each study arm: the specific carbohydrate intake as a percentage of total caloric intake, the mean change and its associated standard deviation for the outcome measures in each group, and the number of participants in each arm. When carbohydrate intake was reported in grams per day, we converted these values into a percentage of total daily caloric intake based on the average calorie consumption reported within those specific studies. For trials that presented carbohydrate intake as a range (e.g, 50% to 60%), we estimated the actual intake percentage using the midpoint between the lower and upper limits.

The chi-square value and I^2 statistics were used to assess the statistical heterogeneity between the included studies. A $p < 0.05$ or an $I^2 > 50\%$ was considered indicative of significant heterogeneity, in which case we used a

random-effects model. Otherwise, a fixed-effects model would be selected. If significant heterogeneity was identified, subgroup analysis was performed to explore the potential source of heterogeneity. Publication bias was assessed with Egger's test and funnel plots. The trim-and-fill method was used to estimate its effect.

We used GRADE[11] protocols to judge the quality of the body of evidence as either high, moderate, low, or very low. More detail on this approach is provided in Supplementary Table 8. Statistical analyses were performed using R version 4.3.2 (R Project for Statistical Computing).[12,13]

RESULTS

Literature search

As depicted in Figure 1, the initial search across the four databases yielded a total of 7,612 articles. After removing duplicate records, the number was reduced to 6,534 studies. Subsequently, two reviewers conducted a preliminary screening of the titles and abstracts, leading to the exclusion of 6,344 papers that did not meet the inclusion criteria.

The subsequent full-text review of the remaining 190 articles was conducted. Upon thorough analysis, an additional 152 articles were excluded for various reasons. Ultimately, a final selection of 38 articles, representing a total of 2,831 participants, was deemed eligible for inclusion in this dose-response meta-analysis.

Characteristics

Characteristics of the studies are summarized in Table 1. Of the 38 trials that satisfied our eligibility criteria, 36 were parallel-arm RCTs and 2 were crossover RCTs, involving a total of 3019 participants diagnosed with type 2 diabetes. The publication period for these trials ranged from 1992 to 2023, and they were included in the current dose-response meta-analysis.[14-51] Among them, 32 studies focused on overweight and obese adults (with a BMI of ≥25 kg/m²), while the remaining six studies included participants with diverse body weights.

The status of glycemic control among participants varied across the trials; 14 trials focused on individuals with good glycemic control, 6 trials investigated those with poor control, and the remaining 18 trials included subjects with a spectrum of glycemic management levels. In terms of dietary interventions compared to control diets, 7 trials utilized a conventional low-fat diet as the control, while 31 trials used either a healthy diet or general dietary advice as the comparative benchmark. On average, the intervention groups consumed 28.5% (±13.1%) of their caloric intake from carbohydrates. Those in the control groups had an average carbohydrate calorie intake of 53.8% (±5.6%). Thus there was a mean difference of 25.3±11.4% between the two groups. Among the various carbohydrate intake diets evaluated, 5 trials implemented ketogenic diets (≤10%), 11 trials used low-carbohydrate diets (10%-26%), and 22 trials investigated moderate-carbohydrate diets (26%-45%). Regarding dietary monitoring, 12 trials assessed and reported actual dietary intake during the intervention period using self-reported data, whereas 26 trials provided prescribed dietary information. In terms of study quality assessment, 12 trials (32%) were deemed to have a low risk of bias, 11 trials (29%) had some concerns regarding bias, and 15 trials (39%) were classified as having a high risk of bias (Supplementary Table 2).

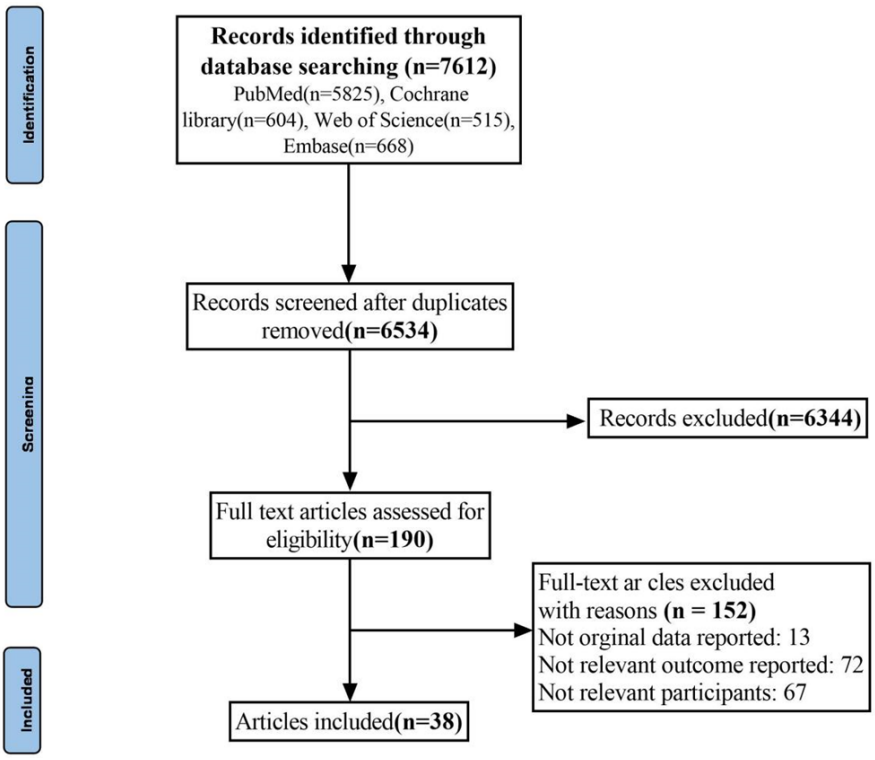


Figure 1. Literature search and study selection process

Table 1. Characteristics of included studies

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Garg, 1992[14]	USA	RCT- cross over	T2D patients (8/8)	aged 52-70	Low carbohydrate diet (35% CHO†,15% Pro‡, 50% Fat)
Daly, 2006[15]	UK	RCT	T2D patients (51/51)	58.2±1.6 / 59.1±1.5	Low carbohydrate diet (34% CHO, 26% Pro, 40% Fat)
Brunerova, 2007[16]	Czech	RCT	T2D patients (14/13)	54.7±3.8 / 51.2±3.3	High-fat diet (45% CHO, 45% Fat, 10% Pro)
Dyson, 2007[17]	UK	RCT	T2D patients (12/14)	55±5 / 50±12	Low carbohydrate diet (17% CHO, 46% Fat, 31% Pro, 6% Alcohol)
Brehm, 2009[18]	USA	RCT	T2D patients (52/43)	56.5±0.8	High MUFA (45% CHO, 40% Fat, 15% Pro)
Davis, 2009[19]	USA	RCT	T2D patients (55/50)	54±6 / 53±7	Low carbohydrate diet (34% CHO, 44% Fat, 22% Pro)
Esposito, 2009[20]	Italy	RCT	T2D patients (108/107)	52.4±11.2 / 51.9±10.7	Low-carbohydrate MED diet(42% CHO, 18% Pro, 40% Fat)
Larsen, 2011[21]	Australia	RCT	T2D patients (53/46)	59.6/58.8	High-protein diet (40% CHO, 30% Fat, 30% Pro)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Garg, 1992[14]	High carbohydrate diet (60% CHO, 15% Pro, 25% Fat)	3	Weight maintenance diet	Participants maintained a constant level of physical activity restricted to level walking
Daly, 2006[15]	Low fat diet (45% CHO, 21% Pro, 33% Fat)	12	Yes(~1300 kcal/day)	Increasing physical activity
Brunerova, 2007[16]	Conventional diet (60% CHO, 30% Fat, 10% Pro)	12	Yes(-600 kcal/day)	Usual physical activity
Dyson, 2007[17]	Healthy eating advice following Diabetes UK nutritional recommendations	52	Yes(-500 kcal/day)	Exercise at moderate intensity for 30 min at least 5 and preferably 7 days per week
Brehm, 2009[18]	High CHO (60% CHO, 25% Fat, 15% Pro)	52	Yes(-250 kcal/day)	Maintain their level of physical activity
Davis, 2009[19]	Low fat diet (50% CHO, 30% Fat, 20% Pro)	52	Yes(-500 kcal/d)	General recommendations to achieve 150 min of physical activity each week
Esposito, 2009[20]	Low fat diet (53% CHO, 19% Pro, 28% Fat)	208	Yes(1800 kcal/day for men and 1500 kcal/day for women)	Walking for a minimum of 30 min per day. With gradual progression toward a goal of 175 min of moderate intensity physical activity per week
Larsen, 2011[21]	High carbohydrate diet (55% CHO, 30% Fat, 15% Pro)	52	Yes(6,400 kJ/day for the first 9 months)	With public health guideline

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Guldbrand, 2012[22]	Sweden	RCT	T2D patients (31/30)	62.7±11 / 61.2±9.5	Low carbohydrate diet (20% CHO, 50% Fat, 30% Pro)
Krebs, 2012[23]	New Zealand	RCT	T2D patients (207/212)	57.7±9.9 / 57.7±9.9	High-protein diet (40% CHO, 30% Fat, 30% Pro)
Luger, 2013[24]	Vienna	RCT	T2D patients (19/20)	61.0±5.7 / 61.0±5.7	High-protein diet (37% CHO, 35% Fat, 25% Pro)
Rock, 2014[25]	USA	RCT	T2D patients (74/76/77)	55.5±9.2 / 56.8±9.3 / 57.3±8.6	1.Low-carbohydrate diet (45% CHO, 30% Fat, 25% Pro)
Yamada, 2014[26]	Japan	RCT	T2D patients (12/12)	63.3 ± 13.5/ 63.2 ± 10.2	Low carbohydrate diet (30% CHO, 45% Fat, 25% Pro)
Goday, 2016[27]	Spain	RCT	T2D patients (45/44)	54.5±8.4 / 54.9±8.8	Very low carbohydrate diet (25-30% CHO, 15% Fat, 50% Pro)
Raygan,2016[28]	Iran	RCT	T2D patients (28/28)	65.2±11.6 / 61.1±9.9	Low carbohydrate diet (43-49% CHO, 36-40% Fat, 10-15% Pro)
Sato, 2016[29]	Japan	RCT	T2D patients (32/30)	58.4±10.0 / 60.5±10.5	Low carbohydrate diet (43% CHO, 35% Fat, 19% Pro)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Guldbrand, 2012[22]	Low fat diet (55-60% CHO, 30% Fat, 10-15% Pro)	52	Yes (1800 kcal/day for men and 1600 kcal/day for women)	No information
Krebs, 2012[23]	High-carbohydrate diet (55% CHO, 30% Fat, 15% Pro)	24	Yes(-500kcal/day)	No information
Luger, 2013[24]	Standard diet (50% CHO, 30% Fat, 17% Pro)	12	Yes(~1200kcal/d)	Maintain current activity level
Rock, 2014[25]	2.Low-fat diet (60% CHO, 20% Fat, 20% Pro) 3.Usual care (55% CHO, 30% Fat, 15% Pro)	52	Yes(-500-1000 kcal/day)	With the goal of 30 min of physical activity on ≥5 days/week.
Yamada, 2014[26]	Conventional calorie-restricted diet (51% CHO, 32% Fat, 16% Pro)	24	Yes(1600 kcal/d)	No
Goday, 2016[27]	Low calorie diet (45-60% CHO, <30% Fat, 15-20% Pro)	12	Yes (Intervention: (600-800 kcal/day), Control diet (-500-1000 kcal/day)	Exercise recommendations
Raygan,2016[28]	High carbohydrate diet(60-65% CHO, 20-25% Fat, 10-15% Pro)	8	Yes (1600-1700 kcal/d)	No information
Sato, 2016[29]	Calorie restricted diet (50-60% CHO, 20% Pro, 20-30% Fat)	24	Yes (1300-1400 kcal/d)	No information

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Stentz, 2016[30]	USA	RCT	T2D patients (12/12)	43.1±1.3 / 41.1±1.7	High-protein diet (34% CHO, 30% Fat, 30% Pro)
Watson, 2016[31]	Australia	RCT	T2D patients (31/28)	54±8 / 55±8	High-protein diet (40% CHO, 30% Fat, 30% Pro)
Saslow, 2017[32]	USA	RCT	T2D patients (16/18)	64.8±7.7 / 55.1±13.5	Very low carbohydrate diet (10% CHO, 25% Pro, 60% Fat)
Renate, 2018[33]	German	RCT	T2D patients (16/20)	63±8	Very low carbohydrate diet (5-10% CHO, 20-30% Pro, 60-70% Fat)
Kimura, 2018[34]	Japan	RCT	T2D patients (12/12)	64.4 ± 3.2 / 66.0 ± 3.2	Mini-low carbohydrate diet(40% CHO, 40% Fat, 25-30% Pro)
Liu, 2018[35]	China	RCT	T2D patients (30/30)	49.7±5.4 / 49.8±5.9	Low-carbohydrate, high-protein diet (42% CHO, 30% Fat, 28% Pro)
Tay, 2018[36]	Australia	RCT	T2D patients (46/47)	58	Low carbohydrate diet (14% CHO, 58% Fat, 28% Pro)
Wang, 2018[37]	China	RCT	T2D patients (24/25)	66.8±9.1 / 61.2±11.7	Low carbohydrate diet (40% CHO, 40% Fat, 20% Pro)
Perna, 2019[38]	Italy	RCT	T2D patients (9/8)	67.8±5.9 / 59.5±9.5	Low carbohydrate diet (27-31% CHO, 22% Fat, 46-50% Pro)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Stentz, 2016[30]	High carbohydrate diet (50% CHO, 22% Fat, 22% Pro)		Yes (-500 kcal/day)	No information
Watson, 2016[31]	High carbohydrate diet (55% CHO, 30% Fat, 15% Pro)	24	Yes (6000-7000 KJ/day)	A minimum of 30 min of moderate intensity aerobic exercise of their choice for at least 5 days per week (150 min/week)
Saslow, 2017[32]	Moderate carbohydrate, calorie-restricted(55% CHO, 20% Pro, 35% Fat)	52	Yes (1300-1400 kcal/d)	Increase their level of physical activity
Renate, 2018[33]	Low-fat diet (50% CHO, 30% Fat, 20% Pro)	3	Yes (Intervention: (1200-1500 kcal/day), Control diet (1000-1000 kcal/day)	No information
Kimura, 2018[34]	Energy controlled diet (55-60% CHO, 20-25% Fat, 15-20% Pro)	12	Yes (25 - 30 kcal/kg of their ideal body weight)	No information
Liu, 2018[35]	Control diet (54% CHO, 29% Fat, 17% Pro)	12	Weight maintenance diet	Participants maintained a light physical activity level
Tay, 2018[36]	High carbohydrate diet (53% CHO, 30% Fat, 17% Pro)	104	Yes (restriction 500-1,000 kcal/day)	60-min structured exercise
Wang, 2018[37]	Low fat diet (55% CHO, 25% Fat, 20% Pro)	12	Usual calorie intake	No information
Perna, 2019[38]	Standard Diet(55-60% CHO, 25-30% Fat, 15-20% Pro)	12	Yes (1,800 kcal/day for males, 1,600 kcal/day for females)	No information

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Skytte, 2019[39]	Denmark	RCT- cross over	T2D patients (24/24)	64±7.7	Carbohydrate reduced high protein (30% CHO, 40% Fat, 30% Pro)
Morris, 2019[40]	UK	RCT	T2D patients (21/12)	69±10 / 64±13	Low carbohydrate diet (25% CHO, 50% Fat, 25% Pro)
Chen, 2020[41]	China-Taiwan	RCT	T2D patients (42/43)	64.1±7.4 / 63.1±10.5	Low carbohydrate diet (less than 90 g/d CHO,)
Evangelista, 2021[42]	USA	RCT	T2D patients (33/43)	57.3±10.1 / 58.0±9.6	High-protein diet (40% CHO, 30% Fat, 30% Pro)
Han, 2021[43]	China	RCT	T2D patients (60/61)	49.1±13.1 / 53.7±13.5	Low carbohydrate diet (14% CHO, 58% Fat, 28% Pro)
Zainordin, 2021[44]	Malaysia	RCT	T2D patients (14/16)	55±13 / 57.5±10	Very low carbohydrate diet (carbohydrate restriction to less than 20g/day)
Dorans, 2022[45]	USA	RCT	T2D patients (75/75)	59.3±7 / 58.6±8.8	Low-carbohydrate diet (23% CHO, 50% Fat, 25% Pro)
Kampmann, 2022[46]	Denmark	RCT	T2D patients (44/20)	57.3±0.9 / 55.2±2.7	Low carbohydrate diet (20% CHO, 50-60% Fat, 25-30% Pro)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Skytte, 2019[39]	Conventional diabetes diet(55% CHO, 33% Fat, 17% Pro)	12	No	No information
Morris, 2019[40]	Usual care (45-60 % CHO, <30% Fat)	12	Yes(800–1000 kcal/day)	Usual physical activity
Chen, 2020[41]	Traditional diabetic diet (50-60% CHO, <30% Fat)	72	Without any restriction to the total energy	Exercise was recommended for both groups and was not a part of the intervention
Evangelista, 2021[42]	Standard-protein diet (55% CHO, 30% Fat, 15% Pro)	12	Yes (-500-800 kcal/day)	Exercise regularly to reduce energy deficiency and promote weight loss and maintenance
Han, 2021[43]	Low fat diet (53% CHO, 30% Fat, 17% Pro)	52	No	No information
Zainordin, 2021[44]	Low protein diet (protein restriction to less than 0.8g/kg/day)	12	No	No information
Dorans, 2022[45]	Usual diet (42% CHO, 37% Fat, 18% Pro)	52	No	No information
Kampmann, 2022[46]	Conventional diabetes diet (50-60% CHO, 30% Fat, 20-25% Pro)	52	Non-calorie-restricted	Free-living

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Li, 2022[47]	China	RCT	T2D patients (24/29)	36.5±13.7 / 37.1±14	carbohydrate30-50g, protein 60g, fat 130g
Thomsen, 2022[48]	Denmark	RCT	T2D patients (33/34)	67.0±8.8 / 66.4±6.9	Conventional diabetes diet(54% CHO, 30% Fat, 16% Pro)
Hansen, 2023[49]	Denmark	RCT	T2D patients (110/55)	57±9 / 55±12	Low carbohydrate diet (20% CHO, 50-60% Fat, 25-30% Pro)
Dening, 2023[50]	Australia	RCT	T2D patients (37/45)	61.3±9.4 / 59.8±9.6	Low carbohydrate diet (10-26% CHO, 45-75% Fat, 15-30% Pro)
Saslow, 2023[51]	USA	RCT	T2D patients (23/25)	60.1±6 / 58.4±8.1	Very low carbohydrate (CHO 20-35g/day)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Li, 2022[47]	Carbohydrate 250-280g, protein 60g, fat 20g	12	Yes (Total calories 1500±50 kcal)	No information
Thomsen, 2022[48]	Carbohydrate reduced high protein (31% CHO, 40% Fat, 29% Pro)	6	No	No information
Hansen, 2023[49]	High carbohydrate diet (50-60% CHO, 20-30% Fat, 20-25% Pro)	52	Calorie-unrestricted	No information
Dening, 2023[50]	Conventional diabetes diet (40% CHO, 40% Fat, 20% Pro)	16	No	No information
Saslow, 2023[51]	DASH diet (55-60% CHO, 20-30% Fat, 10-15% Pro)	16	No	Recommendations for physical activity

CHO: carbohydrate, Pro: protein.

Primary outcome

Table 2 details the effects of different dietary carbohydrate intake on study outcomes. A reduction in carbohydrate intake from 55%-65% to 5% resulted in a 0.39% decrease in HbA1c levels (95% CI: -0.5% to -0.28%; n = 37 trials, 2656 participants; Figure 2). The dose-response meta-analysis demonstrated a linear reduction in HbA1c levels as carbohydrate intake decreased from 65% to 10% (Figure 3).

For every 10% reduction in carbohydrate intake, fasting glucose (FG) levels decreased by 0.55 mmol/L (95% CI: -0.82 to -0.28 mmol/L; n = 20 trials, 1793 participants; Figure 4). A monotonic decrease in FG levels was observed with a reduction in carbohydrate intake (Figure 3).

Secondary outcome

Supplementary Figure 1–3 illustrate the effects of different dietary carbohydrate intake on secondary outcomes. A 10% reduction in carbohydrate intake was associated with a lower BMI (MD: −0.83; 95%CI: −1.27 to −0.38; n = 27 trials involving 1793 subjects; Supplementary Figure 1). BMI showed a significant linear decrease with reduced carbohydrate intake. FI (MD: −2.19; 95%CI: −3.64 to −0.73; n = 11 trials, 707 subjects; Supplementary Figure 2) decreased markedly with a reduction in carbohydrate intake. HOMA−IR (MD: −1.53; 95%CI: −3.09 to 0.03; n = 14 trials, 1050 subjects; Supplementary Figure 3) fell sharply with decreasing carbohydrate intake (Figure 3).

Sensitivity and subgroup analyses

Supplementary Figure 4–13 consist of Baujat plots and influence diagrams for every individual outcome, illustrating the degree of variability among the studies. These visual tools shed light on how much each study individually impacts the overall heterogeneity of outcomes. Results from sensitivity analysis indicate that the primary endpoint remained steadfast and did not experience any material change when any single trial was removed from the evaluation. This indicates that no single study disproportionately influences the primary outcome. The consistency observed underscores the reliability of the meta-analysis conclusions, demonstrating their resilience even when specific trials are excluded. This stability highlights the robust association between carbohydrate intake and glycemic control in T2DM.

Sensitivity analyses accounted for part of the observed heterogeneity in the data. In the HbA1c analysis, seven trials[18,21,35,40,43,46,49] were excluded, partly explaining the heterogeneity (MD: −0.34; 95%CI: −0.40 to −0.28; I^2 = 43.2%). In the fasting glucose analysis, three trials[31,37,43] were excluded, partly explaining the heterogeneity (MD: −0.62; 95%CI: −0.80 to −0.44; I^2 = 58.1%). In the BMI analysis, one trial[43] was excluded due to a control group participant increasing their use of lipid-lowering medications during the study, which partially accounted for the observed heterogeneity (MD: −0.80; 95%CI: −1.27 to −0.33; I^2 = 82.9%). In the fasting insulin analysis, one trial[31] was excluded because it examined a carbohydrate intake difference of approximately 15% between the intervention and control groups, partially accounting for

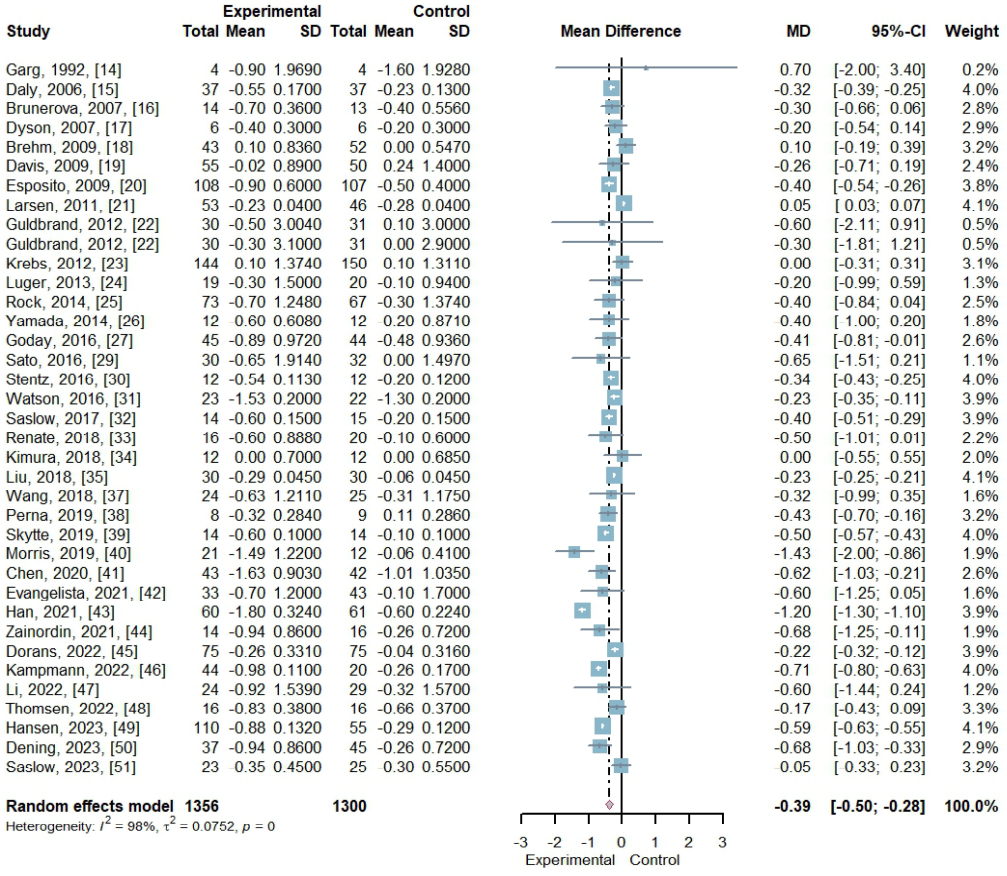


Figure 2. The effect of 10% decrease in carbohydrate intake on HbA1c (%).

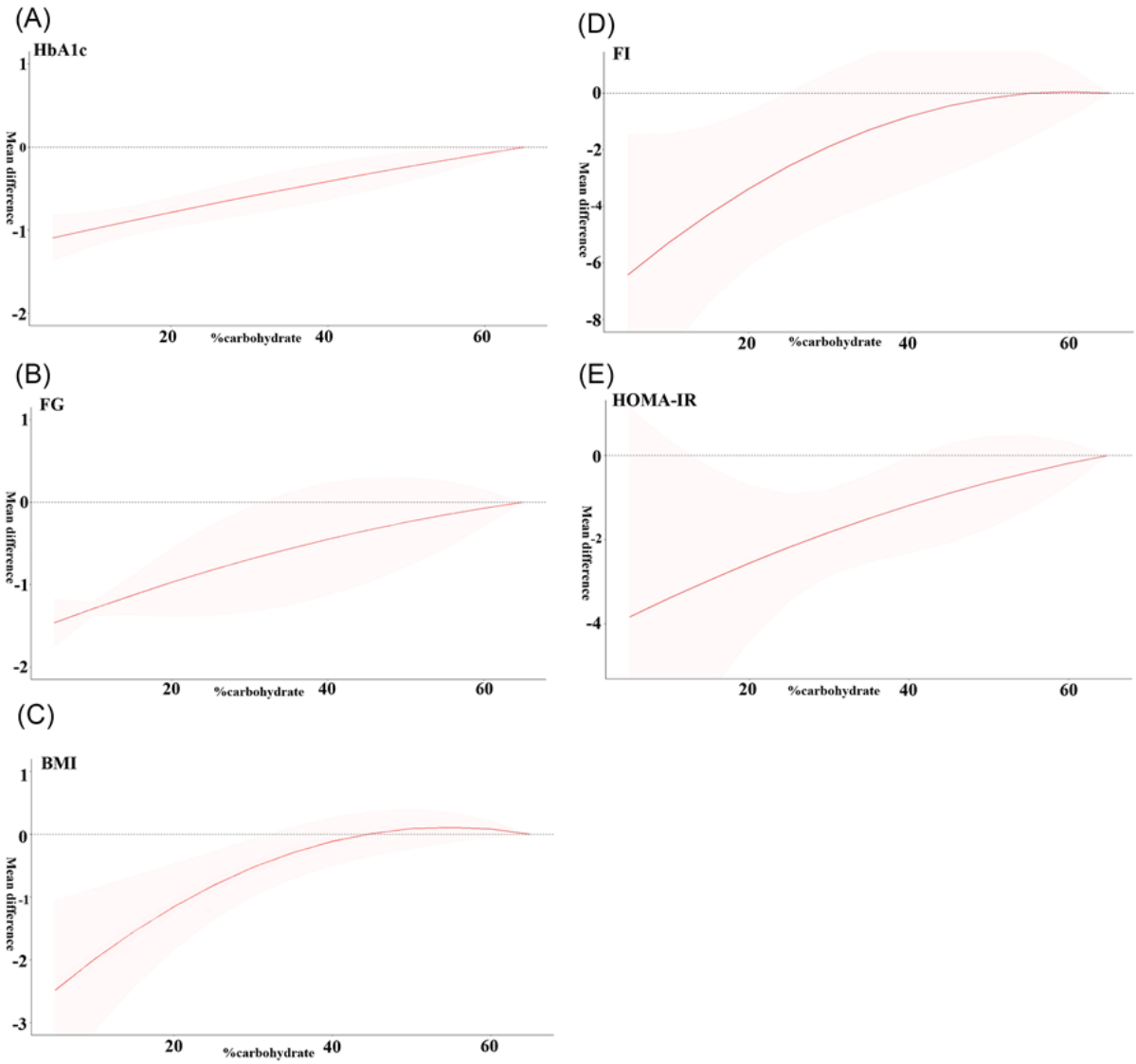


Figure 3. Dose-dependent effect of carbohydrate restriction in patients with type 2 diabetes. Carbohydrate intake was modeled with restricted cubic splines in a multivariate random-effects dose-response model. Pink area represent the 95% confidence intervals for the spline model. The red line represents the linear trend. (a) carbohydrate intake and HbA1c; (b)carbohydrate intake and fasting glucose; (c) carbohydrate intake and BMI; (d) carbohydrate intake and fasting insulin;(e) carbohydrate intake and HOMA−IR

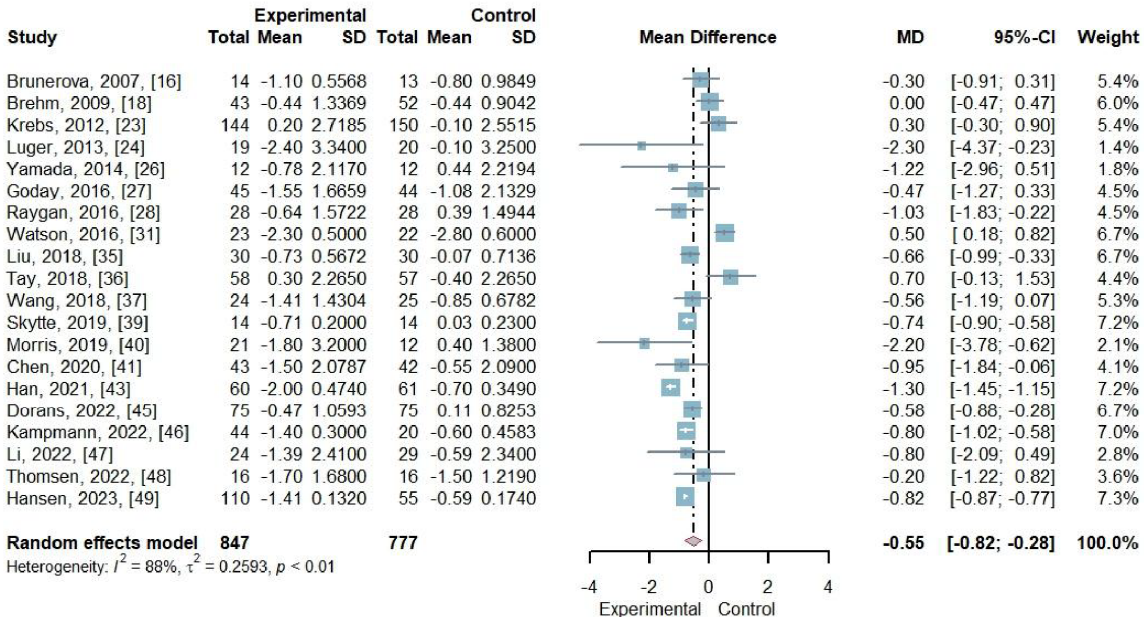


Figure 4. The effect of 10% decrease in carbohydrate intake on fasting glucose (mmol/L).

Table 2. Effects of higher compared with lower intakes of carbohydrate on critical outcomes

	Number of studies	Number of intervention	Number of control	Effect size(95%CI)	GRADE quality
Change in HbA1c (%)	37	1356	1300	MD –0.39 (–0.5 to –0.28)	Moderate
Change in fasting glucose (mmol/L)	20	847	777	MD –0.55 (–0.82 to –0.28)	Moderate
Change in BMI (kg/m^2)	27	896	897	MD –0.83 (–1.27 to –0.38)	High
Change in fasting insulin (pmol/L)	11	366	341	MD –2.19 (–3.64 to –0.73)	Very low
Change in HOMA-IR	14	566	484	MD –1.53 (–3.09 to 0.03)	Very low

Table 3. Summary of the effect of different carbohydrate intake (10% decrease) in T2DM

Carbohydrate intake, % calorie	65% (Ref)	55%	50%	45%	40%	35%	30%	25%	15%	5%
FG, mmol/L	-	-0.15 (-0.56, 0.25)	-0.24 (-0.79, 0.31)	-0.34 (-0.98, 0.30)	-0.45 (-1.13, 0.24)	-0.57 (-1.25, 0.12)	-0.69 (-1.33, -0.05)	-0.83 (-1.38, -0.28)	-1.13 (-1.37, -0.89)	-1.46 (-1.75, -1.17)
HbA1c, %	-	-0.16 (-0.29, -0.02)	-0.24 (-0.42, -0.06)	-0.33 (-.053, -0.12)	-0.42 (-0.64, -0.19)	-0.50 (-0.73, -0.28)	-0.60 (-0.81, -0.38)	-0.69 (-0.89, -0.49)	-0.89 (-1.06, -0.71)	-1.09 (-1.37, -0.82)
BMI, kg/m^2	-	0.11 (-0.13, 0.36)	0.09 (-0.23, 0.40)	0.01 (-0.35, 0.37)	-0.11 (-0.50, 0.28)	-0.29 (-0.71, 0.12)	-0.53 (-0.99, -0.07)	-0.81 (-1.36, -0.27)	-1.54 (-2.43, -0.66)	-2.48 (-3.92, -1.05)
FI, pmol/L	-	-0.01 (-1.58, 1.56)	-0.18 (-2.26, 1.90)	-0.45 (-2.86, 1.97)	-0.82 (-3.42, 1.76)	-1.31 (-3.96, 1.35)	-1.89 (-4.52, 0.73)	-2.59 (-5.20, 0.02)	-4.29 (-7.42, -1.16)	-6.42 (-11.37, -1.47)
HOMA-IR	-	-0.40 (-1.29, 0.48)	-0.64 (-1.74, 0.46)	-0.90 (-2.08, 0.28)	-1.19 (-2.33, -0.05)	-1.49 (-2.53, -0.45)	-1.83 (-2.84, -0.81)	-2.18 (-3.45, -0.91)	-2.96 (-5.64, -0.27)	-3.83 (-8.79, 1.13)

FG, fasting glucose; HbA1c, glycated hemoglobin; FI, fasting insulin; HOMA−IR, Homeostatic Model Assessment of Insulin Resistance..

the observed heterogeneity (MD: −2.58; 95%CI: −3.99 to 0.89; I^2 = 67.7%).

Subgroup analyses evaluated the potential effects of trial duration, risk of bias, caloric restriction, physical activity, behavioral support, baseline status, dietary reporting, intervention strategies, and protein intake percentage. A greater reduction was observed in trials with an intervention duration of ≤6 months (HbA1c [MD: -0.45; 95%CI: -0.57 to -0.32; p < 0.01; n = 28 trials], FG [MD: -0.68; 95%CI: -0.95 to -0.41; p < 0.01; n = 16 trials], BMI [MD: -0.89; 95%CI: -1.42 to -0.36; p < 0.01; n = 21 trials], FI [MD: -2.15; 95%CI: -4.07 to -0.21; p < 0.01; n = 8 trials], HOMA-IR [MD: -1.93; 95%CI: -4.1 to 0.24); p < 0.01; n = 10 trials]). When the duration of intervention was >*6* months, the decline was somewhat diminished (HbA1c [MD: -0.22; 95%CI: -0.41 to -0.04; p < 0.01; n = 9 trials], FG [MD:0.04; 95%CI: -0.55 to 0.63; p = 0.05; n = 4 trials], BMI [MD: -0.60; 95%CI: -1.36, 0.15; p = 0.05; n = 6 trials], FI [MD: -2.55; 95%CI: -3.75 to -1.34; p = 0.32; n = 3 trials], HOMA-IR [MD: -0.38; 95%CI: -0.76 to 0.01; p < 0.01; n = 4 trials]).

The effect of a low dietary carbohydrate intake was more pronounced in patients with poor glycemic control. The effect of dietary intervention was similar across different control groups and dietary protein intake groups. However, the effect was less pronounced in the calorie-restricted subgroup compared to the no-calorie-restricted subgroup. The exercise subgroup showed a greater improvement in BMI than the non-exercise subgroup, although other outcomes were less effective than in the non-exercise subgroup (Supplementary Table 3−7).

Publication bias

Supplementary Figure 14–20 show the assessment of funnel plot asymmetry. There was an asymmetry between the HbA1c funnel plot and the HOMA−IR funnel plot, which was confirmed by Egger' s test (p < 0.01; p = 0.04). The number of missing studies was 0 after the Trim−and−fill method, indicating that the results of HbA1c and HOMA−IR were stable. To reduce publication selection bias, we performed a meta−regression approximation, PET−PEESE.[52] The results are HbA1c (MD: -0.39; 95%CI: -0.51 to -0.28, p < 0.01) and HOMA-IR (MD: -1.55; 95%CI: -1.72 to -1.38, p < 0.01).

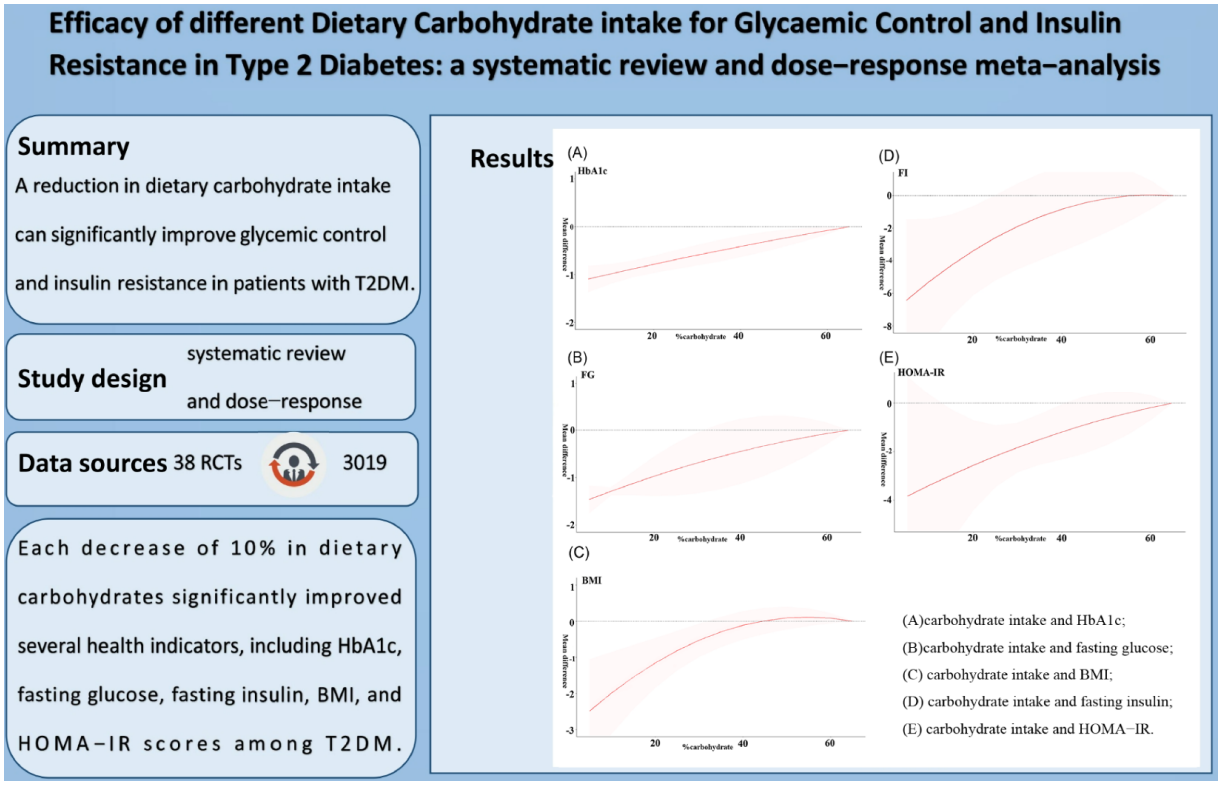
DISCUSSION

This present dose-response meta-analysis scrutinized the impact of varying levels of carbohydrate intake in diets on glycemic control and insulin resistance outcomes among T2DM. Our findings indicate that each 10% reduction in dietary carbohydrates significantly improves several health indicators, including HbA1c, FG, FI, BMI, and HOMA-IR scores in individuals with T2DM. The intervention group showed significant improvements compared to the control group, with a 0.39% reduction in HbA1c, a 0.55 mmol/L decrease in FG, a 0.83 kg/m² decline in BMI, a 2.19 pmol/L drop in FI, and a notable 1.53-point reduction in HOMA-IR scores. The application of GRADE criteria indicated that the quality of evidence for BMI was high, demonstrating robust and reliable data. The quality of evidence for HbA1c and fasting glucose levels was rated as moderate, reflecting a reasonable level of certainty in the outcomes. In contrast, the evidence for FI and HOMA-IR was rated as very low, underscoring the need for further rigorous research to validate these findings.

Notably, a prospective study identified a U-shaped relationship between carbohydrate intake and the risk of new-onset diabetes, with the lowest risk observed at 49–56% of total energy derived from carbohydrates.[53] In contrast to this observation, our findings specifically demonstrated that a lower-carbohydrate diet is associated with more pronounced improvements, particularly in reducing BMI and lowering FI levels in individuals with T2DM. Furthermore, an inverse L-shaped correlation was identified between high-quality carbohydrate intake and the risk of new-onset diabetes, whereas a J-shaped correlation was observed with low-quality carbohydrate intake.[53] Adopting a diet that restricts carbohydrate intake while controlling the quality of carbohydrates may offer significant therapeutic benefits for glycemic regulation in T2DM. As impaired glucose tolerance advances, pancreatic β-cell function can decline due to the detrimental effects of glucose toxicity.[2] Lowering blood glucose concentrations may help alleviate glucose toxicity, thereby improving β-cell function. This strategy holds the potential to achieve remission or even reversal of T2DM.

Network meta-analyses indicate that low-carbohydrate diets are particularly effective in reducing HbA1c levels, while Mediterranean diets with moderate carbohydrate intake are optimal for lowering FG. Both low- and moderate-carbohydrate diets have been shown to enhance blood glucose control effectively.[54] Our research highlights that a low-carbohydrate diet (<26% carbohydrates), particularly a ketogenic diet, yields more pronounced improvements. However, while a ketogenic diet may reduce glycemic variability, it simultaneously increases the risk of hypoglycemia. This underscores the need for heightened monitoring through continuous glucose monitoring systems, which may lead to higher healthcare costs.[55] Consequently, considering these trade-offs, a very low-carbohydrate ketogenic diet may not be the most practical option for long-term adherence when its benefits are weighed against potential risks. The relationship between BMI and carbohydrate intake followed a subtle inverse U-shaped curve, indicating that BMI tends to increase with carbohydrate intakes of 45–60%, compared to an intake of 65%. Notably, both HbA1c and FG levels continue to decrease with reduced carbohydrate consumption. Furthermore, a study revealed that weight loss does not directly correlate with improved blood glucose control; a low-carbohydrate diet can enhance glycemic control even in the absence of weight loss.[56] This suggests that reducing carbohydrate intake may have a direct effect on blood sugar regulation, independent of changes in BMI.

Our subgroup analyses indicated that the improvements in all parameters tend to diminish after six months, a finding that aligns with previous meta-analyses.[3,57] The Chinese Guidelines for Medical Nutrition Therapy for Patients with Diabetes (2022 Edition) also note that a low-carbohydrate diet lacks identified long-term benefits.[58] This underscores the need for more robust evidence on the long-term benefits of reducing dietary carbohydrate



Graphical abstract.

intake. Interestingly, exercise did not significantly impact outcomes compared to the non-exercise subgroups, except for a more pronounced reduction in BMI. This suggests that weight loss is not the primary mechanism driving improvements in glycemic control and insulin resistance; rather, the reduction in carbohydrate intake plays a crucial role. Improved glycemic control, which can occur before significant weight loss, is likely due to lower glucose levels resulting from reduced carbohydrate consumption, thereby alleviating glucose toxicity and enhancing glycemic management.[2] The subgroup findings also indicated that basic behavioral support alone may be insufficient to ensure adherence. Stricter diet compliance and direct provision of meals yielded better results than self-managed diets. Consistently meeting prescribed dietary targets led to superior outcomes, reinforcing the benefits of carbohydrate reduction. However, these interventions may face practical challenges, highlighting the need for structured guidance or direct intervention to ensure compliance and maximize health benefits.

The conventional pairwise comparison approach used in standard meta-analyses has limitations in providing strong evidence for clinical decision-making and in identifying the optimal dosage of an intervention.[4,59–62] Moreover, existing meta-analyses have shown that low-carbohydrate diets do not lead to any statistically or clinically significant increases in adverse events compared to healthy diets over medium to long-term periods.[63–66] Our study concludes that even a modest 10% reduction in dietary carbohydrate intake can have a small yet positive effect on glycemic control and insulin resistance, with the effect becoming more pronounced as the degree of carbohydrate reduction increases. To put this into context, a 10% reduction in carbohydrate intake equates to approximately 50g of carbohydrates daily. This provides a more accessible and comprehensible approach for guiding patients through dietary therapy or education, enhancing patient adherence and potentially facilitating the remission or even reversal of T2DM.

Strengths and limitations

This study is the first to investigate the relationship between carbohydrate intake and insulin resistance using a dose-response meta-analysis of randomized controlled trial data. This approach sets our study apart from previous meta-analyses, which predominantly examined the effects of carbohydrate reduction on glycemic control and insulin resistance in T2DM.[3,4,63] To minimize the impact of low-glycemic index diets on our findings, we excluded studies explicitly promoting or implementing such diets, focusing instead on trials involving mixed diets. Data transformations were carefully applied to address discrepancies across the trials, ensuring consistent and reliable comparisons. Our meta-analysis included three distinct categories of carbohydrate intake levels: moderate-carbohydrate diets (22 trials), low-carbohydrate diets (11 trials), and very low-carbohydrate diets (5 trials). This diverse range of dietary interventions allowed for a robust dose-response meta-analysis, assessing the effects of varying degrees of carbohydrate restriction on glycemic control and insulin resistance in T2DM.

The limitations of our study include the lack of a comprehensive evaluation of adverse events across all included studies, despite previous reviews suggesting no significant or clinically meaningful increase in such events with low-carbohydrate diets. Hence, limiting our ability to fully assess the long-term safety profiles of such diets. The forest plots revealed substantial heterogeneity in the

data, likely driven by variations in effect sizes (ranging from strong to moderate to weak) rather than differences in effect direction (increase or decrease). This is supported by the consistency in directional outcomes across most trials.

Conclusion

In summary, the present dose-response meta-analysis offers novel insights into the impact of varying dietary carbohydrate intake levels on T2DM. Our findings show that reducing carbohydrate consumption can lead to meaningful improvements in short-term glycemic control and contribute to the reversal of insulin resistance in T2DM. A consistent negative linear correlation was observed between the percentage of carbohydrates in the diet and HbA1c, FG, BMI, FI, and HOMA-IR values.

It is noteworthy that improvements in glycemic management and insulin sensitivity were most pronounced when the intervention period was less than six months. These results highlight the potential importance of tailored carbohydrate restriction strategies in managing diabetes, particularly during the early stages of treatment or lifestyle modification. However, further research is needed to clarify the long-term effects and determine the optimal carbohydrate intake thresholds for sustainable glycemic control and overall health outcomes in T2DM.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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