Efficacy of different dietary carbohydrate intake for glycaemic control and insulin resistance in type 2 diabetes: A systematic review and dose-response meta-analysis

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ABSTRACT

Background and Objectives: The aim of this study was to elucidate the dose-response relationship between dietary carbohydrate consumption and the amelioration 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. The primary outcome: glycated hemoglobin (HbA1c), fasting glucose (FG). 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 with the highest carbohydrate intake collected (65%), carbohydrate intake decreased to 5%, and for each 10% reduction in carbohydrate intake, HbA1c (MD: 0.39%; 95%CI: -0.5 to -0.28%), FG (MD: 0.55mmol/L; 95%CI: -0.82 to -0.28mmol/L), BMI (MD: -0.83kg/m2; 95%CI: -1.27 to -0.38kg/m2), FI (MD: -2.19pmol/L; 95%CI: -3.64 to -0.73pmol/L), HOMA-IR (MD: -1.53; 95%CI: -3.09 to 0.03). **Conclusions:** Reducing dietary carbohydrate intake significantly ameliorates glycemic control and insulin resistance in individuals with type 2 diabetes. A linear reduction in carbohydrate intake was observed, with the intervention demonstrating significant effects within the initial 6 months. These effects were observed to attenuate beyond this period. Notably, the improvements in glycemic parameters were not significantly influenced by the presence or absence of calorie restriction.

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] As a result, meticulous attention to and management of the glycemic response to dietary carbohydrates are essential for improving postprandial glucose levels and optimizing overall glycemic regulation in T2DM.

Historically, guidelines for diabetes management have recommended a carbohydrate intake constituting 45% to 60% of total calories. Recent reviews underscore the efficacy of a spectrum of carbohydrate-restricted diets in the management of T2DM. This spectrum encompasses moderate carbohydrate diets, which comprise 26-45% of total calories (approximately 130-230g daily), low-carbohydrate diets that account for 10-26% of total calories (50-130 g daily), and ketogenic diets , characterized by a threshold of ≤10% of total calories (20–50g daily). Multiple systematic reviews and meta-analyses of interventional studies have yielded evidence in favor of the short-term benefits of reduced carbohydrate diets on glycemic control among T2DM.[3–5] However, these studies are primarily involve simple pairwise comparisons, which are insufficient to determine the optimal dosage 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.

MATERIALS AND METHODS

The present systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), as detailed in Supplementary Table 1.

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 2.

Selection criteria

The inclusion criteria were as follows: 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

The exclusion criteria were as follows: 1) reporting on alternative dietary treatments 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 meticulously determined.

For each study group, the change from baseline was meticulously 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 9. Statistical analyses were performed using R version 4.3.2 (R Project for Statistical Computing).[12,13]

RESULTS

Results of the 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 with meticulous attention to detail. Upon thorough analysis, an additional 152 articles were excluded for various reasons. Ultimately, a final selection of 38 articles, representing a collective total of 2,831 participants, was deemed eligible for inclusion in this dose-response meta-analysis, thus establishing the basis of our study.

Characteristics

Critical data is 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 specifically 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, with 14 trials specifically focusing on individuals with good glycemic control, 6 trials concentrating on those with poor control, and the remaining 18 trials including 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 employed 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, compared to the control groups, which had an average carbohydrate calorie intake of 53.8% (±5.6%), yielding 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 applied 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 (Table S3 for detailed ratings).

Primary outcome

Table 2 details the effects of different dietary carbohydrate intake on study outcomes. A reduction of 10% in carbohydrate intake, compared to an intake ranging from 55% to 65%,and further minimized to 5%, led to a decrease in HbA1c levels by 0.39% (95% CI: -0.5% to -0.28%; n = 37 trials, 2656 participants; Figure 2). The dose-response meta-analysis revealed a linear reduction in HbA1c levels, notably from a carbohydrate intake of 65% down to 10% (as depicted in Figure 4).

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

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 exhibited a pronounced linear decrease as carbohydrate intake was reduced. Similarly, FI (MD: −2.19; 95%CI: −3.64 to − 0.73; n = 11 trials, 707 subjects; Figure S2). FI fell sharply with decreasing carbohydrate intake. HOMA−IR (MD: −1.53; 95%CI: −3.09 to 0.03; n = 14 trials, 1050 subjects; Supplementary Figure 3). HOMA−IR fell sharply with decreasing carbohydrate intake (Figure 4).

Sensitivity and subgroup analyses

Supplementary Figure 4–13 consist of Baujat plots and influence diagrams for every individual outcome, effectively illustrating the degree of variability among the studies. These visual tools shed light on how much each study individually impacts the overall heterogeneity in outcomes. The results stemming from a sensitivity analysis indicate that the primary endpoint remained steadfast and did not experience any material change when any single trial was systematically removed from the evaluation. This implies that no one particular study exerts undue sway over the primary outcome measure. This consistency suggests that the conclusions drawn from the meta−analysis are resilient and dependable, holding up even with the exclusion of specific trials. The stability observed here reinforces the solidity and robustness of the relationship 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[16,18,31,33,33,41,47] were excluded, partly explaining the heterogeneity (MD: −0.34; 95%CI: −0.40 to −0.28; I2 = 43.2%). In the fasting glucose analysis, three trials 18,36,37 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 trial18 in which a control group member increased the use of lipid−lowering medications during the trial was excluded, partly explaining the heterogeneity (MD: −0.80; 95%CI: −1.27 to −0.33; I^2 = 82.9%). In the fasting insulin analysis, one trial37 that examined a difference of approximately 15% in carbohydrate intake between the intervention and control groups was excluded, partly explaining the heterogeneity (MD: −2.58; 95%CI: −3.99 to 0.89; I^2 = 67.7%).

Subgroup analyses were performed to examine the potential effects of trial duration, risk of bias, caloric restriction, physical activity, behavioral support, baseline status, dietary reporting, intervention-group measures, and percentage protein intake. The reduction was greater in the subgroup based on 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 intervention time＞6 months, the decline was reduced to a certain extent, 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 improvement effect of different dietary carbohydrate intake on patients with poor glycemic control was more pronounced. The effect of dietary intervention was similar between different control groups and different dietary protein intake groups. However, the effect in the calorie−restricted subgroup was not as good as that in the no−calorie−restricted subgroup. The exercise subgroup improved BMI much more than the non−exercise subgroup, but other outcomes were less effective than the non−exercise subgroup. (The specific data are detailed in Supplementary Table 4−8).

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 decrease of 10% in dietary carbohydrates significantly improved several health indicators, encompassing HbA1c, FG, FI, BMI, and HOMA-IR scores in T2DM. The intervention group exhibited marked improvements over the control group, as evidenced by a 0.39% decrease in HbA1c, a 0.55 mmol/L reduction in FG, a 0.83 kg/m² decrease in BMI, a 2.19 pmol/L drop in FI, and a significant reduction of 1.53 points in HOMA-IR scores. The application of GRADE criteria revealed that the quality of evidence for BMI was high, reflecting robust and reliable data. The evidence quality for HbA1c and fasting glucose levels was categorized as moderate, indicating a reasonable degree of certainty

in the outcomes. However, the evidence for FI and HOMA-IR was deemed to be of very low quality, highlighting the necessity for further rigorous research to reinforce these findings.

Notably, a prospective study highlighted a U-shaped association between carbohydrate consumption and the risk of new-onset diabetes, with minimal risk at 49-56% of energy from total carbohydrate intake.[53] Contrasting with this observation, our results specifically demonstrated that a lower carbohydrate diet is associated with more favorable improvement effects, particularly in reducing BMI and lowering FI levels for T2DM. Moreover, there was an inverse L-shaped correlation between the intake of high-quality carbohydrates and the risk of new-onset diabetes, while 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] By lowering blood glucose concentrations, it may be possible to alleviate glucose toxicity and thereby improve β-cell function. This approach could potentially lead to remission or even the reversal of T2DM.

Network meta-analyses have demonstrated that low-carbohydrate diets are particularly effective at reducing HbA1c levels, whereas Mediterranean diets with moderate carbohydrates are optimal for lowering FG. Both low- and moderate-carbohydrate diets have been shown to effectively enhance blood glucose control.[54] Our research underscores that a low-carbohydrate diet (<26% carbs), particularly ketogenic diet, yields more pronounced improvements. Notably, while a ketogenic diet may reduce glycemic variability, it also concurrently increases the risk of hypoglycemia. This necessitates heightened monitoring through the use of continuous glucose monitoring systems, potentially elevating healthcare costs.[55] Consequently, considering these trade-offs, a very low-carbohydrate ketogenic diet might not be the most feasible option for long-term adherence if the benefits are weighed against the potential risks. The relationship between BMI and carbohydrate intake exhibited a subtle inverse U-shaped curve, suggesting that BMI tends to increase at carbohydrate intakes between 45% and 60%, compared to an intake of 65%. Importantly, both HbA1c and FG levels continue to decrease with reduced carbohydrate consumption. A study revealed that weight loss doesn't directly correlate with improved blood glucose control; a low-carb diet can improve glycemic control even in the absence of weight loss.[56] This implies that the reduction of carbohydrates may exert a direct influence 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 highlights the need for more robust evidence regarding the long-term benefits of reducing dietary carbohydrate intake. Interestingly, exercise did not significantly alter outcomes compared to non-exercise subgroups, with the exception of a more pronounced reduction in BMI. This suggests that weight loss is not the primary mechanism driving the improvements in glycemic control and insulin resistance; instead, the reduction in carbohydrate intake is pivotal. Improved glycemic control, which can occur before substantial weight loss, is likely due to the decreased glucose levels resulting from reduced dietary carbohydrates, thereby alleviating glucose toxicity and enhancing glycemic management.[2] The subgroup findings also indicated that basic behavioral support may be insufficient for ensuring 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 might encounter practical challenges, necessitating structured guidance or direct intervention to ensure compliance and maximize health benefits.

The conventional pairwise comparison approach used in standard meta-analyses has its limitations in providing compelling evidence for clinical decision-making and identifying the optimal dosage of an intervention.[4,59–62] Moreover, existing meta-analyses have indicated that low-carbohydrate diets do not result in 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 contextualize this, a 10% reduction in carbohydrate intake equates to approximately 50g of carbohydrates daily. Thus, we can utilize more accessible and comprehensible information to guide patients through dietary therapy or education, thereby enhancing patient adherence and potentially facilitating remission or even reversal of T2DM.

Strengths and limitations

The present study represents a pioneering endeavor to investigate the relationship between carbohydrate intake and insulin resistance through a dose-response meta-analysis, leveraging data from randomized controlled trials. This approach distinguishes our work from previously

published meta-analyses that have focused on the impact of carbohydrate reduction on glycemic control and insulin resistance in T2DM.[3,4,63] To mitigate the influence of low-glycemic index diets on our results, we deliberately excluded studies that explicitly advocated or implemented such diets. Instead, we concentrated on trials that employed mixed diets. Data transformations were meticulously performed to reconcile discrepancies among the various trials, thereby facilitating consistent and reliable comparison. Our meta-analysis covered three distinct categories of carbohydrate intake levels: moderate-carbohydrate diets, as represented in 22 trials; low-carbohydrate diets, included in 11 trials; and very low-carbohydrate diets, covered in 5 trials. This comprehensive spectrum of dietary interventions allowed us to conduct a robust dose-response meta-analysis, scrutinizing the effects of varying degrees of carbohydrate restriction on glycemic control and insulin resistance outcomes in T2DM.

The limitations of our study are as follows: Although previous reviews have indicated no significant or clinically meaningful increase in adverse events with low-carbohydrate diets, our study did not conduct a comprehensive evaluation of these outcomes across all included studies. This omission limits our ability to fully understand the long-term safety profiles of such diets. The forest plots demonstrated substantial heterogeneity within the data, which is likely attributable to variations in effect sizes (ranging from strong to moderate to weak) rather than differences in the direction of the effects (i.e., increase or decrease). This inference is supported by the observation that the majority of trial results were consistent in their directional outcomes.

Conclusion

In summary, the present dose−response meta−analysis provides novel insights into the impact of varying dietary carbohydrate intake levels on T2DM. Our findings demonstrate that a reduction in carbohydrate consumption can lead to meaningful enhancements 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 the improvements in glycemic management and insulin sensitivity were most notable when the intervention period was less than six months. These results underscore the potential importance of tailored carbohydrate restriction strategies in the management of diabetes, especially during the early stages of treatment or lifestyle modification interventions. Nonetheless, further research is warranted to clarify the long−term

effects and to determine the optimal carbohydrate intake thresholds for sustainable glycemic control and favorable overall health outcomes in T2DM.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Characteristics of included studies

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Garg, 1992	USA	RCT- cross over	T2D patients (8/8)	aged 52-70	Low carbohydrate diet (35% CHO[†],15% Pro[‡], 50% Fat)
Daly, 2006	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	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	UK	RCT	T2D patients (12/14)	55±5 / 50±12	Low carbohydrate diet (17% CHO, 46% Fat, 31% Pro, 6% Alcohol)
Brehm, 2009	USA	RCT	T2D patients (52/43)	56.5±0.8	High MUFA (45% CHO, 40% Fat, 15% Pro)
Davis, 2009	USA	RCT	T2D patients (55/50)	54±6 / 53±7	Low carbohydrate diet (34% CHO, 44% Fat, 22% Pro)
Esposito, 2009	Italy	RCT	T2D patients (108/107)	52.4±11.2 / 51.9±10.7	Low-carbohydrate MED diet(42% CHO, 18% Pro, 40% Fat)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Garg, 1992	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	Low fat diet (45% CHO, 21% Pro, 33% Fat)	12	Yes (~1300 kcal/day)	Increasing physical activity
Brunerova, 2007	Conventional diet (60% CHO, 30% Fat, 10% Pro)	12	Yes (-600 kcal/day)	Usual physical activity
Dyson, 2007	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	High CHO (60% CHO, 25% Fat, 15% Pro)	52	Yes (-250 kcal/day)	Maintain their level of physical activity
Davis, 2009	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	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

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Larsen, 2011	Australia	RCT	T2D patients (53/46)	59.6/58.8	High-protein diet (40% CHO, 30% Fat, 30% Pro)
Guldbrand, 2012	Sweden	RCT	T2D patients (31/30)	62.7±11 / 61.2±9.5	Low carbohydrate diet (20% CHO, 50% Fat, 30% Pro)
Krebs, 2012	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	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	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	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	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)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Larsen, 2011	High carbohydrate diet (55% CHO, 30% Fat, 15% Pro)	52	Yes (6,400 kJ/day for the first 9 months)	With public health guideline
Guldbrand, 2012	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	High-carbohydrate diet (55% CHO, 30% Fat, 15% Pro)	24	Yes (-500kcal/day)	No information
Luger, 2013	Standard diet (50% CHO, 30% Fat, 17% Pro)	12	Yes (~1200kcal/d)	Maintain current activity level
Rock, 2014	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	Conventional calorie-restricted diet (51% CHO, 32% Fat, 16% Pro)	24	Yes (1600 kcal/d)	No
Goday, 2016	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

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Raygan,2016	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	Japan	RCT	T2D patients (32/30)	58.4±10.0 / 60.5±10.5	Low carbohydrate diet (43% CHO, 35% Fat, 19% Pro)
Stentz, 2016	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	Australia	RCT	T2D patients (31/28)	54±8 / 55±8	High-protein diet (40% CHO, 30% Fat, 30% Pro)
Saslow, 2017	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	German	RCT	T2D patients (16/20)	63±8	Very low carbohydrate diet (5-10% CHO, 20-30% Pro, 60-70% Fat)
Kimura, 2018	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)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Raygan,2016	High carbohydrate diet(60-65% CHO, 20-25% Fat, 10-15% Pro)	8	Yes (1600-1700 kcal/d)	No information
Sato, 2016	Calorie restricted diet (50-60% CHO, 20% Pro, 20-30% Fat)	24	Yes (1300-1400 kcal/d)	No information
Stentz,2016	High carbohydrate diet (50% CHO, 22% Fat, 22% Pro)		Yes (-500 kcal/day)	No information
Watson, 2016	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	Moderate carbohydrate, calorie-restricted(55% CHO, 20% Pro, 35% Fat)	52	Yes (1300-1400 kcal/d)	Increase their level of physical activity
Renate ,2018	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	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

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Liu, 2018	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	Australia	RCT	T2D patients (46/47)	58	Low carbohydrate diet (14% CHO, 58% Fat, 28% Pro)
Wang, 2018	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	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)
Skytte, 2019	Denmark	RCT- cross over	T2D patients (24/24)	64±7.7	Carbohydrate reduced high protein (30% CHO, 40% Fat, 30% Pro)
Morris, 2019	UK	RCT	T2D patients (21/12)	69±10 / 64±13	Low carbohydrate diet (25% CHO, 50% Fat, 25% Pro)
Chen, 2020	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	USA	RCT	T2D patients (33/43)	57.3±10.1 / 58.0±9.6	High-protein diet (40% CHO, 30% Fat, 30% Pro)

References	Control	Duration (weeks)	Calorie restriction (amount)	Physical activity
Liu, 2018	Control diet (54% CHO, 29% Fat, 17% Pro)	12	Weight maintenance diet	Participants maintained a light physical activity level
Tay, 2018	High carbohydrate diet (53% CHO, 30% Fat, 17% Pro)	104	Yes (restriction 500-1,000 kcal/day)	60-min structured exercise
Wang, 2018	Low fat diet (55% CHO, 25% Fat, 20% Pro)	12	Usual calorie intake	No information
Perna, 2019	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
Skytte, 2019	Conventional diabetes diet(55% CHO, 33% Fat, 17% Pro)	12	No	No information
Morris, 2019	Usual care (45-60 % CHO, <30% Fat)	12	Yes (800–1000 kcal/day)	Usual physical activity
Chen, 2020	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	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

CHO: carbohydrate, Pro: protein.

Table 1. Characteristics of included studies (cont.)

References	Country	Study design	Sample size (intervention / control)	Age (intervention / control)	Intervention
Han, 2021	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	Malaysia	RCT	T2D patients (14/16)	55±13 / 57.5±10	Very low carbohydrate diet (carbohydrate restriction to less than 20g/day)
Dorans, 2022	USA	RCT	T2D patients (75/75)	59.3±7 / 58.6±8.8	Low-carbohydrate diet (23% CHO, 50% Fat, 25% Pro)
Kampmann, 2022	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)
Hansen, 2022	Denmark	RCT	T2D patients (110/55)	57±9 / 55±12	Low carbohydrate diet (20% CHO, 50-60% Fat, 25-30% Pro)
Li, 2022	China	RCT	T2D patients (24/29)	36.5±13.7 / 37.1±14	carbohydrate30-50g, protein 60g, fat 130g
Thomsen, 2022	Denmark	RCT	T2D patients (33/34)	67.0±8.8 / 66.4±6.9	Conventional diabetes diet(54% CHO, 30% Fat, 16% Pro)
Dening, 2023	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	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
Han, 2021	Low fat diet (53% CHO, 30% Fat, 17% Pro)	52	No	No information
Zainordin, 2021	Low protein diet (protein restriction to less than 0.8g/kg/day)	12	No	No information
Dorans, 2022	Usual diet (42% CHO, 37% Fat, 18% Pro)	52	No	No information
Kampmann, 2022	Conventional diabetes diet (50-60% CHO, 30% Fat, 20-25% Pro)	52	Non-calorie-restricted	Free-living
Hansen, 2022	High carbohydrate diet (50-60% CHO, 20-30% Fat, 20-25% Pro)	52	Calorie-unrestricted	No information
Li, 2022	Carbohydrate 250-280g, protein 60g, fat 20g	12	Yes (Total calories 1500±50 kcal)	No information
Thomsen, 2022	Carbohydrate reduced high protein (31% CHO, 40% Fat, 29% Pro)	6	No	No information
Dening, 2023	Conventional diabetes diet (40% CHO, 40% Fat, 20% Pro)	16	No	No information
Saslow, 2023	DASH diet(55-60% CHO, 20-30% Fat, 10-15% Pro)	16	No	Recommendations for physical activity

CHO: carbohydrate, Pro: protein.

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/m2	-	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..

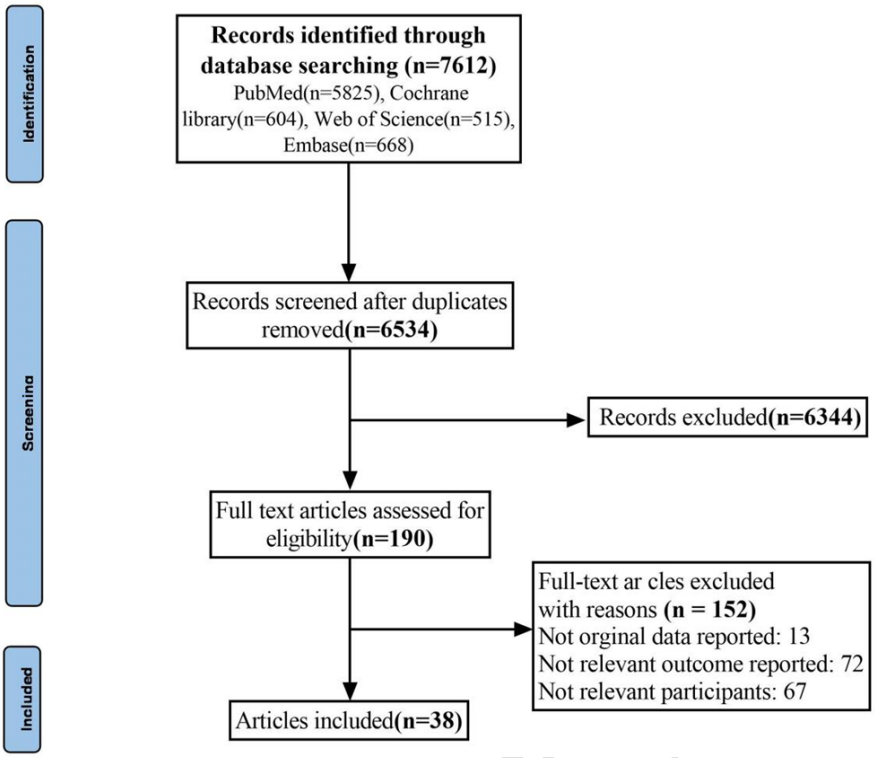


Figure 1. Literature search and study selection process

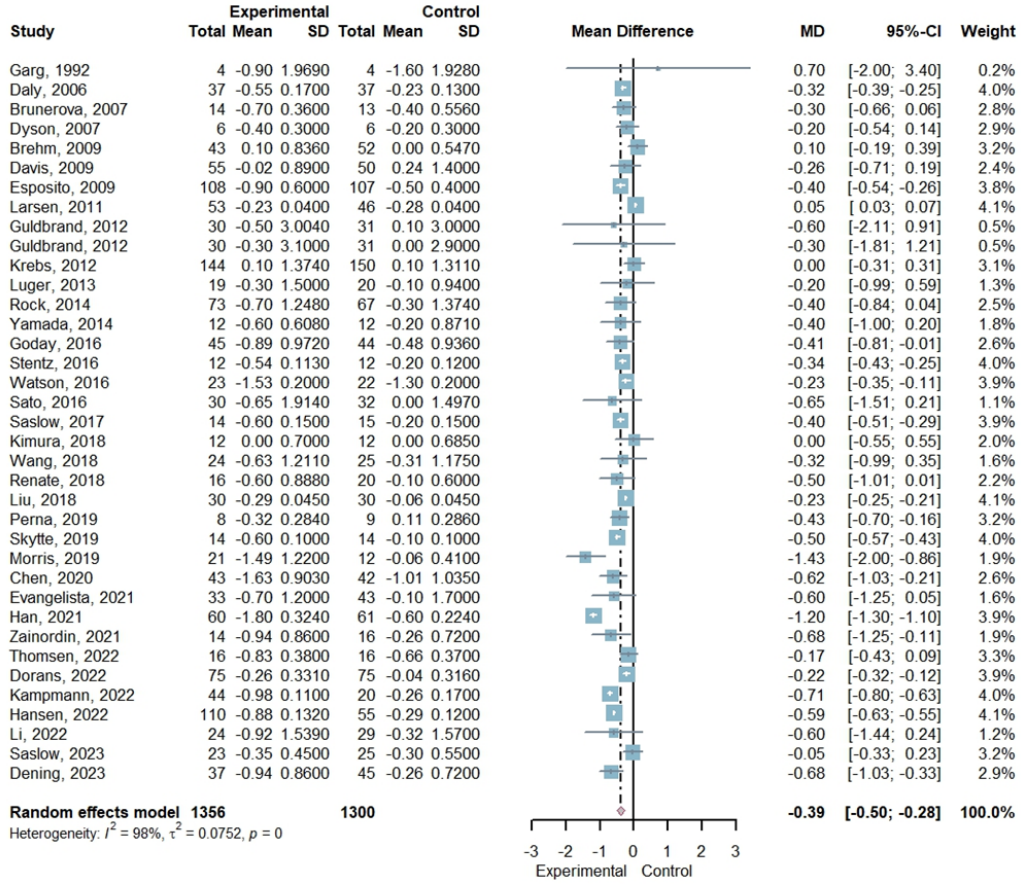


Figure 2. The effect of 10% decrease in carbohydrate intake on HbA1c (%)

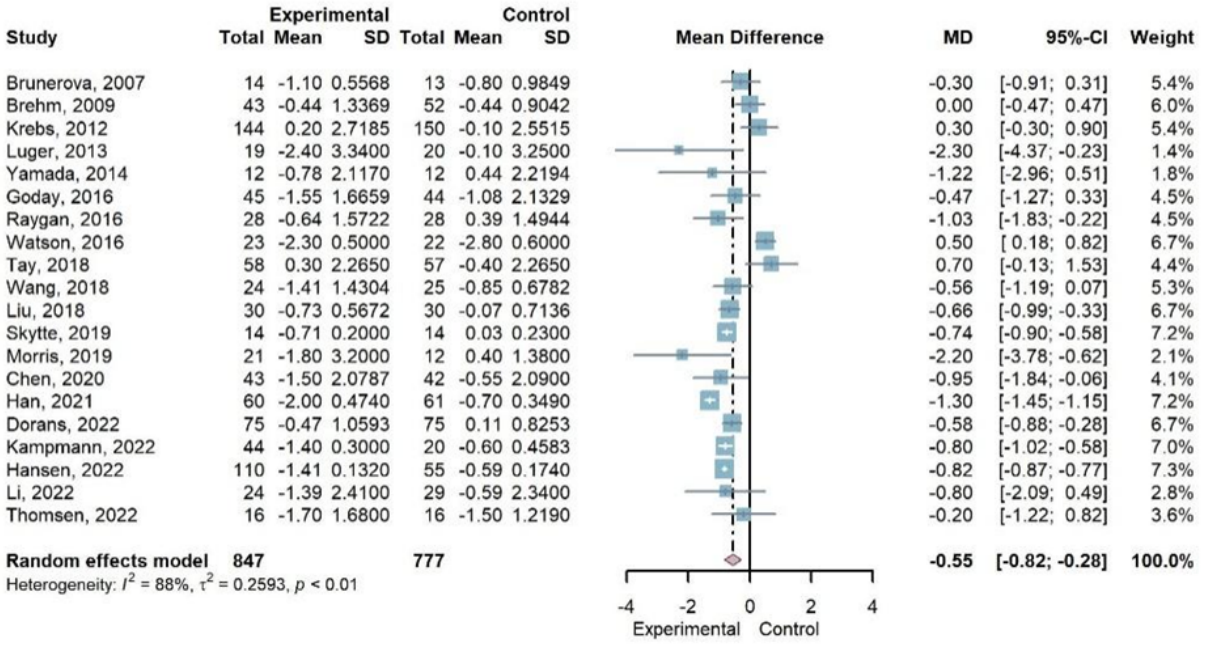


Figure 3. The effect of 10% decrease in carbohydrate intake on fasting glucose (mmol/L)

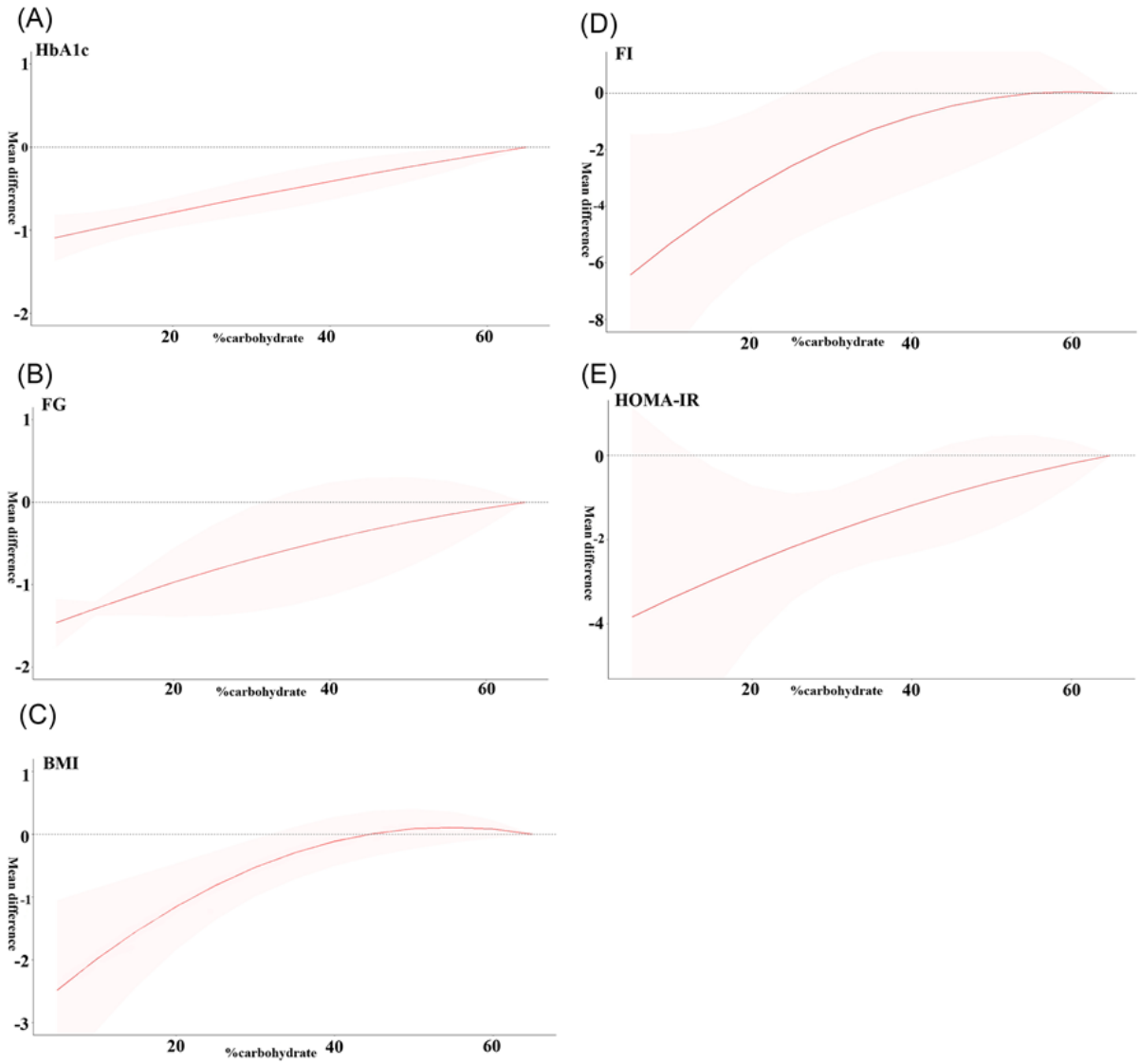
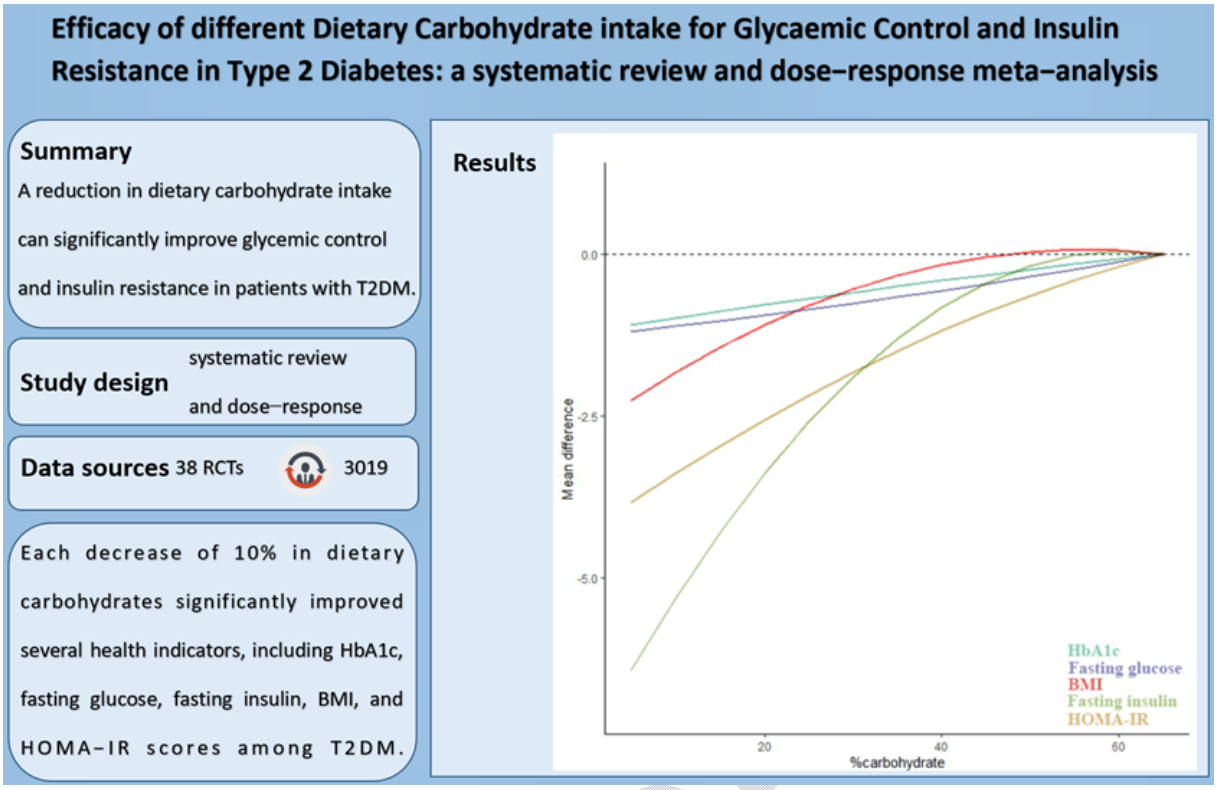


Figure 4. Dose-dependent effect of carbohydrate restriction in patients with type 2 diabetes. Carbohydrate intake was modeled with restricted cubic splines in a multivariate random-effects dose-response model. Pink area represent the 95% confidence intervals for the spline model. The red line represents 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



Graphical abstract