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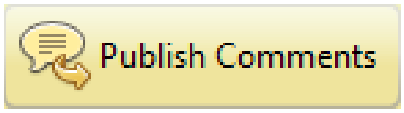

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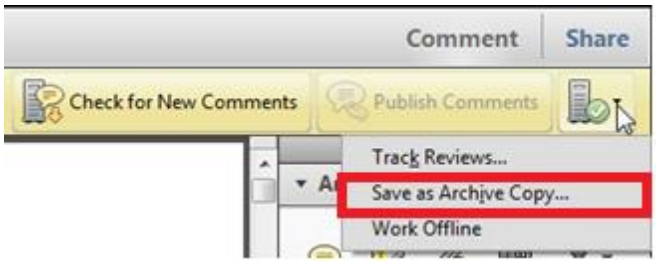

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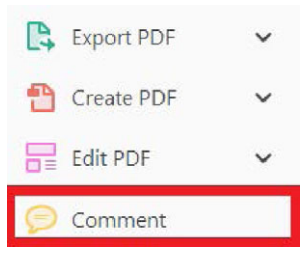

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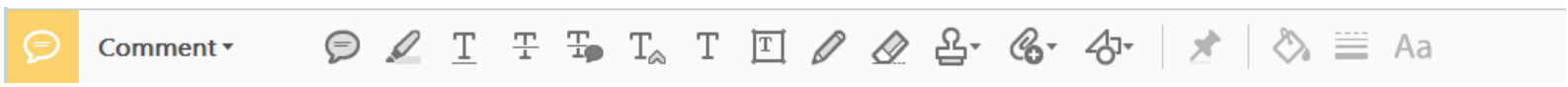

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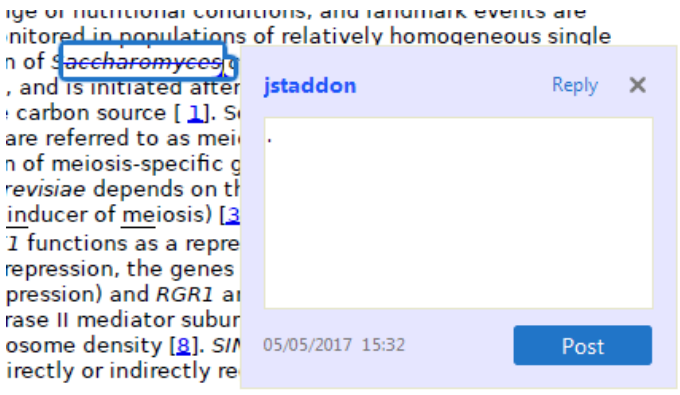

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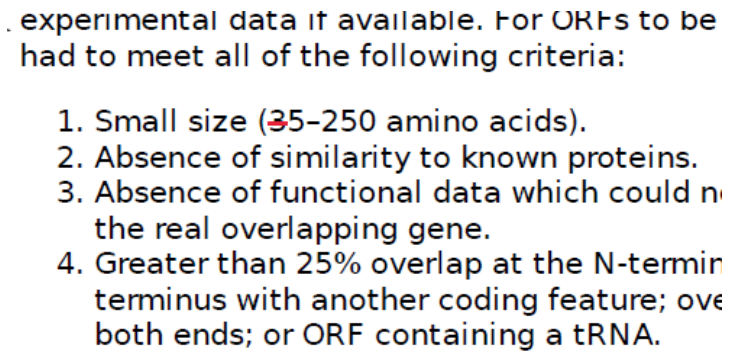

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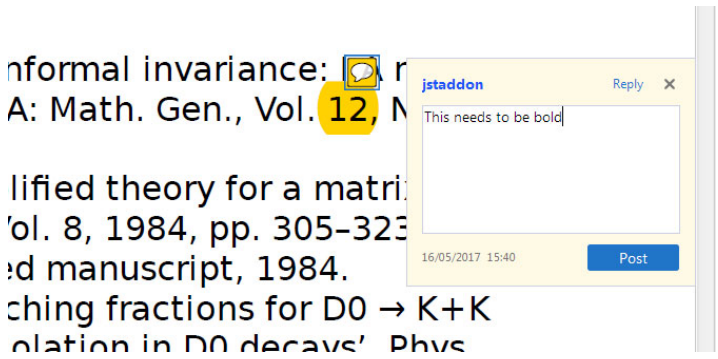

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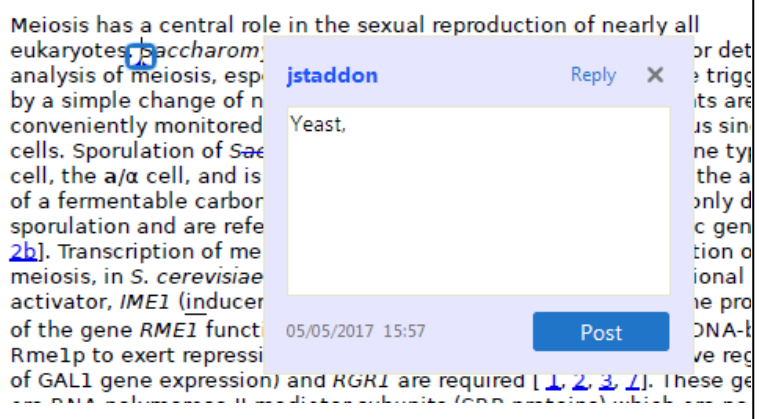

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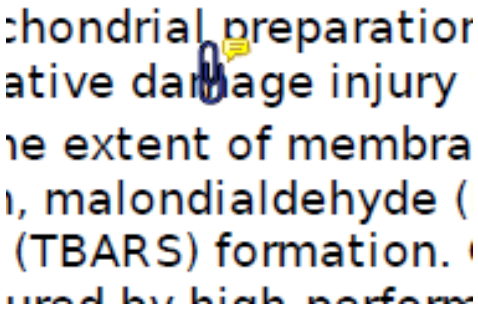

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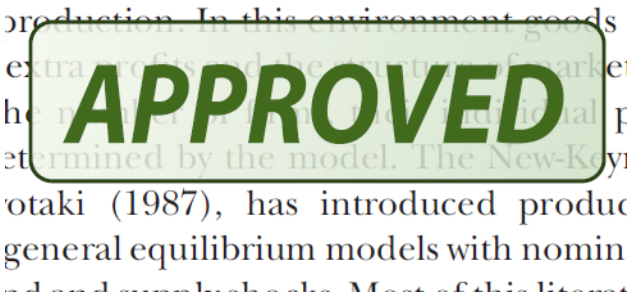

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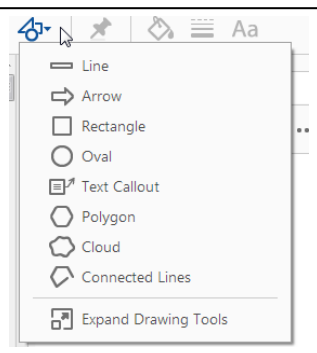

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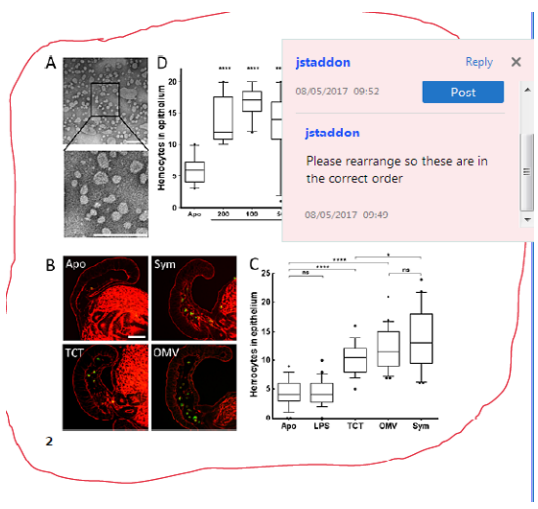

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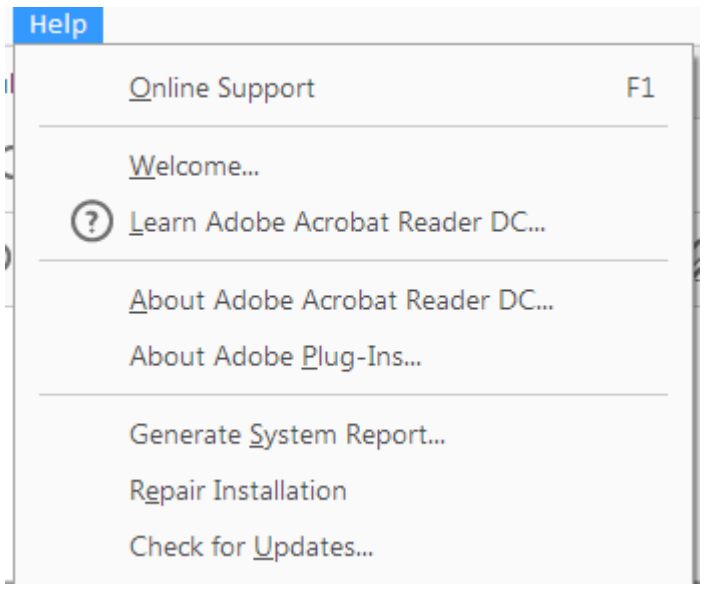

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REVIEW ARTICLE

Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis

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Aims: This systematic review and meta-analysis (registration number: CRD42013005825) compares the effects of low carbohydrate diets (LCDs) on body weight, glycaemic control, lipid profile and blood pressure with the effects of higher carbohydrate diets (HCDs) in adults with type 2 diabetes.

Methods: MEDLINE, EMBASE, CENTRAL, CINAHL, Food Science Source and SweMed+ databases were systematically searched to identify randomized controlled trials (duration ≥3 months) investigating the effects of an LCD compared to an HCD in the management of type 2 diabetes. Data were extracted and pooled using a random effects model and were expressed as mean differences and risk ratio. Subgroup analyses were undertaken to examine the effects of duration of intervention, extent of carbohydrate restriction and risk of bias. The certainty of evidence was assessed using GRADE.

Results: Of the 1589 studies identified, 23, including 2178 participants, met inclusion criteria. Reductions were slightly greater with LCDs than with HCDs for HbA1c (−1.0 mmol/mol; CI, −1.9, −0.1 [−0.09%; CI, −0.17, −0.01]) and for triglycerides (−0.13 mmol/L; CI, −0.24, −0.02). Changes in weight, HDL- and LDL-cholesterol, total cholesterol and blood pressure did not differ significantly between groups. Subgroup analyses suggested that the difference in HbA1c was evident only in studies with a duration of ≤6 months and with a high risk of bias.

Conclusions: The proportion of daily energy provided by carbohydrate intake is not an important determinant of response to dietary management, especially when considering longer term trials. A range of dietary patterns, including those traditional in Mediterranean countries, seems suitable for translating nutritional recommendations for individuals with diabetes into practical advice.

KEYWORDS

dietary intervention, dyslipidaemia, glycaemic control, meta-analysis, systematic review, type 2 diabetes

1 | INTRODUCTION

Dietary advice is generally accepted as a cornerstone of the management of type 2 diabetes (T2DM).[1] More than 80% of all patients presenting with T2DM are overweight or obese,[2,3] and recommendations relating to energy intake and physical activity aimed at weight management are a core component of treatment for T2DM worldwide.[4–7] However, advice regarding the macronutrient composition has varied over time.[8] With occasional exceptions, carbohydrate restriction was a key component of diabetic dietary prescriptions for much of the 20th Century. In the 1960s it became evident that CHD rates were exceptionally high in individuals with diabetes and the high intake of fat, predominantly saturated fat, associated with the reduction in carbohydrate was presumed to be a contributory factor. This observation, together with demonstration of the beneficial effects of dietary fibre on glycaemic control and blood lipids in the 1970s, led to a change in the nutritional approach. Consumption of fibre-rich, low-glycaemic index carbohydrates was encouraged and total carbohydrate intake was liberalized in advice to individuals with diabetes, as well as populations at large.[4,9–14]

More recent reports have suggested the potential of appreciable reductions in carbohydrate to facilitate weight reduction and improve glycaemic control, insulin sensitivity, blood pressure, HDL-cholesterol and triglyceride levels to a greater extent than higher carbohydrate diets.[15–19] However, three recent meta-analyses of trials undertaken in individuals with T2DM reached different conclusions regarding the merits of carbohydrate restriction in this patient group.[16,20,21] In order to provide information for an update of current European Guidelines for the management and prevention of diabetes, we have undertaken a systematic review and meta-analysis that attempts to circumvent the criticisms that have been directed at earlier attempts to aggregate the relevant trials.[22,23] More specifically, we wanted to investigate whether a low-carbohydrate diet (LCD) improved weight and metabolic control more than a higher carbohydrate diet in patients with type 2 diabetes.

2 | MATERIALS AND METHODS

This systematic review was carried out according to Cochrane recommendations,[24] and was reported in line with the PRISMA Statement[25] (Table S1). The protocol for this review was prospectively registered in PROSPERO (CRD42013005825).

2.1 | Search strategy and study selection

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Food Science Source and SweMed + for RCTs published between 1983 and January 2016. Our search terms were: (diet OR carbohydrate-restricted OR low carbohydrate diet OR dietary carbohydrates OR ketogenic diet OR Atkins diet OR diabetic diet) AND (type 2 diabetes OR diabetes mellitus OR type 2 OR diabetes OR non-insulin dependent diabetes mellitus), using MeSH terms when available. We also searched the reference list of identified studies and performed forward citation searches to consider studies not identified by our online search.

We included randomized, controlled trials of parallel or cross-over design with a duration of more than 3 months in adults with type 2 diabetes. We had no restrictions regarding minimum number of included participants. Co-morbidity was accepted, but studies including individuals with impaired glucose tolerance and/or type 1 diabetes were included only whenever separate data for patients with type 2 diabetes were provided. To be included, trials must have compared a diet below to a diet above 40% total energy (E%) from carbohydrate. Complex interventions with the potential to interfere with the effect of the dietary intervention, such as parenteral administration or promotion of physical activity, were excluded.

We included studies written in English, Danish, Norwegian and Swedish. One author ~~(H. K. H.)~~ screened all titles and abstracts and excluded obviously irrelevant records. For the remaining records, full-text articles were obtained and assessed independently for inclusion by two authors ~~(A. M. A. and H. K. H.)~~. Any disagreements were resolved by consensus.

2.2 | Data extraction and risk of bias

From each study we extracted the name of the first author, year of publication, study design, study duration, participant details, intervention diet details, markers of compliance with diets, and outcomes measured. The following outcomes were considered: weight, HbA1c, lipids, blood pressure and compliance with dietary intervention. Data were extracted by one author ~~(H. K. H.)~~ and verified by a second author ~~(A. M. A.)~~.

We assessed risk of bias for the main items suggested by Cochrane[24]: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. For each study and outcome, two authors (~~H. K. H. and A. M. A.~~) independently rated the seven domains as low, unclear or high risk of bias.

We applied the following criteria to assess overall risk of bias for each study and outcome.

- Low risk: No high risk of bias, and not more than two unclear risks of bias
- High risk: Two or more high risks of bias, one high and more than one unclear risk, or more than four unclear risks of bias

The remaining articles were classified as unclear risk of bias.

Because of the nature of delivery of dietary interventions, blinding of participants and study personnel who provided dietary advice was not possible. Hence, this item was not considered when assessing the overall risk of bias.

2.3 | Data synthesis and analysis

Results were summarized qualitatively and, whenever applicable, results from available studies were combined in meta-analysis using Review Manager (RevMan Version 5.3. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We expected clinical heterogeneity among studies, and chose the random-effects model. The weighting of individual trials was defined by inverse variance and mantel-haenszel methods for continuous and dichotomous outcomes, respectively. We calculated the mean difference (MD) for continuous outcomes, whereas dichotomous effect sizes were expressed in terms of a risk ratio (RR). For trials with multiple dietary arms, we pooled data for the higher-carbohydrate diet groups to create one control group.[24] Crossover trials were not included in the meta-analysis because of the short intervention period and possible carryover effect. The HbA1c unit was converted from % to mmol/mol using a conversion calculator (http://www.ngsp.org/convert2.asp).

Meta-analyses were considered to be associated with heterogeneity when the I^2 value was above 50% and/or the P value of the Cochrane Q test was less than 0.10,[24] and subgroup analysis was used to explore possible reasons for the suggested heterogeneity. In particular, we conducted *post-hoc* subgroup and sensitivity analyses to explore the impact of study duration (≤6 vs ≥12 months), varying carbohydrate content in the LCD-group (very low-carbohydrate diets

(VLCD): 21-70 g carbohydrates and moderate LCD: 30-40 E% carbohydrates)[15] and risk of bias (low vs high).

Two authors (~~A. M. A. and H. K. H.~~) independently graded[26] the certainty of the evidence for diets of lower carbohydrate content when compared with diets of higher carbohydrate content in the management of type 2 diabetes. We assessed publication bias for a given outcome by inspection of funnel plots.

3 | RESULTS

3.1 | Search results and characteristics of the included studies

Out of 1589 studies identified through database searches and cross reference list matching, 23 studies were included in the review[27–49] (Figure 1). The main reasons for exclusion were diet intervention not being low-carbohydrate; duration of intervention being less than 3 months; study sample consisting of individuals without type 2 diabetes and studies using a non-randomized and/ or non-controlled trial design (Table S2).

The total number of participants from the 23 articles was 2178, 1061 of whom were in the low-carbohydrate group and 1194 of whom were in the control group. Two studies included participants with and without type 2 diabetes.[31,34] From these studies, only data on the participants with type 2 diabetes were extracted. The follow-up periods ranged from 3 months[28,29,32,33,38,45,46] to over 3 years.[30] Studies were published between 1994[27] and 2014.[46–49] Eight studies were conducted in North America,[27,30,31,33,35–37,46] five in Europe,[32,38,42,45,47] five in Australia,[28,29,41,44,48] one in New Zealand,[43] three in Israel[34,39,40] and one in Japan.[49] A randomized crossover design was used in four studies,[27–29,38] and 19 studies were parallel randomized control trials with one or two control groups.[30–37,39–49]

A summary of findings from the included studies is presented in Table 1. Twelve studies reported having included individuals who were either overweight or obese.[31–35,37,39–41,43,44,48] Physical activity was not specifically addressed in any of the studies, but several trials promoted general recommendations for physical activity.

The LCD was compared to low-fat diets,[31–34,37,42,47,49] to diets typical of standard diabetes care,[38–40,45] to high-carbohydrate diets,[27,29,41] to low-protein diets,[30,44] to a standard protein diet,[48] to Mediterranean diets,[34,39] to high-carbohydrate, low-fat diets,[28,43] to a high wheat-fibre diet,[46] to low-glycaemic index diets[35,36] or to a high-glycaemic index diet.[36] The recommended amount of dietary carbohydrates in the low-carbohydrate interventions ranged from 5%[35] to 40%[27–29,33,41,43–45,48] of the total energy intake. Among the 17 studies that assessed actual intake of carbohydrates throughout the study period, all but one[48] found that the difference in carbohydrate intake was statistically significant between the LCD-group and the comparator.[28,29,32,33,36–43,45–47,49] In six of the low-carbohydrate interventions,[28,29,33,39,47,48] and in ten of the comparator diets,[28,29,33–35,39,40,47–49] it was intended that participants consumed energy-restricted diets that ranged from approximately 5000 kJ (1200 kcal)[40] to 7500 KJ (1800 kcal)[34] per day. Fifteen studies emphasized that weight reduction was a goal of the dietary

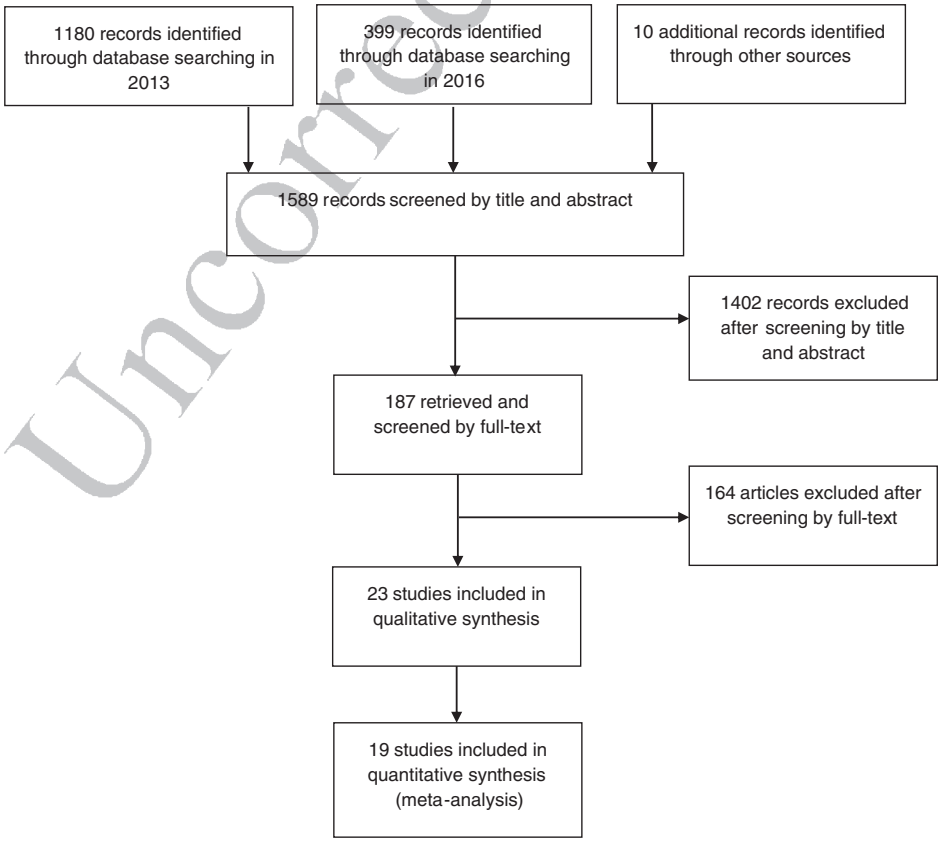


FIGURE 1 PRISMA study eligibility flow chart

TABLE 1 Characteristics and summary of findings of studies selected for inclusion in the review

Study details	Study design	Participants randomized	LCD	Comparator	Outcome	Duration	Weight	HbA1c	Serum lipids	Blood pressure	Compliance with LCD presented as mean ± SD
MODERATE LOW-CARBOHYDRATE DIETS											
Brinkworth et al.,[44] Australia (2004)	Randomized controlled trial	66 obese type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 E% protein	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition[a]	16 months	Weight reduced ($P < 0.01$). No difference between groups	NS	HDL increased ($P < 0.001$). No difference between groups	DBP reduced ($P < 0.05$). Greater reduction in SBP and DBP with the LCD ($P = 0.04$ and < 0.008)[b]	NA
Elhayany et al.,[39] Israel (2010)[c]	Randomized controlled trial	259 overweight type 2 diabetes patients	35 E% CH 45 E% fat 15–20 E% protein	50–55 E% CH 30 E% fat 20 E% protein	Weight, HbA1c LDL, HDL TG, TC Compliance by food records and attrition	12 months	Weight reduced ($P < 0.001$). No difference between groups	HbA1c reduced ($P < 0.001$). Greater reduction with the LCD ($P = 0.021$)[d,e]	LDL, HDL, TG and TC improved ($P < 0.001$). Greater improvements in LDL[d], HDL[d e] and TG[d] with the LCD ($P = 0.036$, <0.001 and < 0.001)	NA	42 E% CH
Facchini et al.,[30] USA (2003)	Randomized controlled trial	191 type 2 diabetes patients with renal failure	35 E% CH 30 E% fat 25–30 E% protein 5–10 E% ethanol	65 E% CH 25 E% fat 10 E% protein	Weight HbA1c LDL, HDL, TC	Mean follow-up 3.0 ± 1.8 years	NS	NS	HDL increased[f] No difference between groups	NA	NA
Garg et al.,[27] USA (1994)	Randomized crossover trial	21 type 2 diabetes patients	40 E% CH 45 E% fat 15 E% protein	55 E% CH 30 E% fat 15 E% protein	LDL, HDL TG, TC	14 weeks	NA	NA	TG reduced ($P = 0.03$). No difference between groups	NA	NA
Jenkins et al.,[46] Canada (2014)	Randomized controlled trial	141 type 2 diabetes patients	39 E% CH[g] 37 E% fat[g] 20 E% protein[g]	49 E% CH[g] 27 E% fat[g] 20 E% protein[g]	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition	3 months	Weight reduced ($P < 0.05$). No difference between groups	HbA1c reduced ($P < 0.05$). No difference between groups	LDL, HDL, TG and TC reduced ($P < 0.05$). Greater reduction in LDL, HDL, TC and TG with the LCD ($P < 0.01$, =0.04, <0.01 and = 0.18)	SBP and DBP reduced ($P < 0.05$). No difference between groups	Not applicable[g]
Jönsson et al.,[38] Sweden (2009)	Randomized crossover trial	13 non-insulin treated type 2 diabetes patients	32 E% CH 39 E% fat 24 E% protein	42 E% CH 34 E% fat 20 E% protein	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records	3 months	Weight reduced (p = 0.005 and 0.01). Greater reduction in weight with the LCD ($P = 0.01$ and 0.04)	HbA1c reduced ($P < 0.001$). Greater reduction with the LCD ($P = 0.02$)	TG reduced ($P = 0.003$). Greater improvements in HDL and TG with the LCD ($P = 0.03$ and 0.003)	SBP reduced ($P = 0.048$). Greater reduction in DBP with the LCD ($P = 0.03$)	32 ± 7 E% CH 39 ± 5 E% fat 24 ± 3 E% protein
Krebs et al.,[43] New Zealand (2012)	Randomized controlled trial	419 overweight type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 E% protein	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	24 months	Weight reduced ($P < 0.001$). No difference between groups	NS[f]	NS[f]	NS	46 ± 7 E% CH 33 ± 6 E% fat 21 ± 4 E% protein

(*Continues*)

TABLE 1 (Continued)

Study details	Study design	Participants randomized	LCD	Comparator	Outcome	Duration	Weight	HbA1c	Serum lipids	Blood pressure	Compliance with LCD presented as mean ± SD
Larsen et al.,[41] Australia (2011)	Randomized controlled trial	108 overweight and obese type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 E% protein	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	12 months	Weight reduced ($P < 0.001$). No difference between groups	HbA1c reduced ($P < 0.001$). No difference between groups	HDL and TG improved[f]. No difference between groups	NS[f]	42 E% CH 31 E% fat 27 E% protein
Luger et al.,[45] Austria (2013)	Randomized controlled trial	44 insulin treated type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15%% protein	Weight HbA1c LDL, HDL, TG Blood pressure Compliance by food records and attrition	3 months	Weight reduced ($P < 0.001$). No difference between groups	HbA1c reduced ($P = 0.05$). No difference between groups	TG reduced ($P = 0.01$). No difference between groups	DBP reduced ($P = 0.005$). No difference between groups	38 ± 7 E% CH 35 ± 6 E% fat 26 ± 5 E% protein
McLaughlin et al.,[33] USA (2007)	Randomized controlled trial	29 overweight, diet-treated type 2 diabetes patients	40 E% CH 45 E% fat 15 E% protein	60 E% CH 25 E% fat 15 E% protein	Weight LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	3 months	Weight reduced ($P < 0.001$). No difference between groups	NA	TG reduced ($P = 0.008$). No difference between groups	NS	43 E% CH 38 E% fat 19 E% protein
Pedersen et al.,[48] Australia (2014)	Randomized controlled trial	76 overweight type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	50 E% CH 30 E% fat 20 E% protein	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition	12 months	Weight reduced ($P < 0.001$). No difference between groups	HbA1c reduced ($P = 0.01$). No difference between groups	HDL and TG improved ($P < 0.01$ and < 0.001). Greater increase in LDL with the LCD ($P = 0.05$)	Greater reduction in DBP with the LCD ($P = 0.01$)	197 ± 16 g CH (40 E%) 78 ± 7 g fat (35 E%) 131 ± 10 g protein (26 E%)
Walker et al.,[28] Australia (1995)	Randomized crossover trial	24 type 2 diabetes patients	40 E% CH 40 E% fat	59 E% CH 21 E% fat	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records	3 months	Weight reduced ($P < 0.005$). No difference between groups	NS	NS	NS	40 ± 1 E% CH 36 ± 1 E% fat 22 ± 1 E% protein
Walker et al.,[29] Australia (1999)	Randomized crossover trial	34 post-menopausal women with type 2 diabetes	40 E% CH 40 E% fat	60 E% CH 20 E% fat	Weight HbA1c HDL, TG, TC Compliance by food records	3 months	Weight reduced ($P < 0.01$). No difference between groups	NS[h]	NS[h]	NA	43 ± 5 E% CH 33 ± 5 E% fat 21 ± 2 E% protein
Wolever et al.,[36] Canada (2008)	Randomized controlled trial	162 diet-treated type 2 diabetes patients	39 E% CH[g] 40 E% fat[g] 19 E% protein[g]	47 E% CH[g] 31 E% fat[g] 20 E% protein[g] 52 E% CH[g] 27 E% fat[g] 21 E% protein[g]	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition	12 months	Weight reduced ($P = 0.003$). No difference between groups	HbA1c increased ($P < 0.0001$). No difference between groups	LDL reduced ($P = 0.0079$). No difference between groups	DBP reduced ($P = 0.0080$). Greater reduction in DBP with the LCD ($P = 0.020$)	Not applicable[g]

(*Continues*)

TABLE 1 (Continued)

Study details	Study design	Participants randomized	LCD	Comparator	Outcome	Duration	Weight	HbA1c	Serum lipids	Blood pressure	Compliance with LCD presented as mean ± SD
Yamada et al.,[49] Japan (2014)	Randomized controlled trial	24 type 2 diabetes patients	<130–70 g/day CH (33 E%)	50–60 E% CH <25 E% fat <20 E% protein	Weight, HbA1c LDL, HDL, TG Blood pressure Compliance by food records and attrition	6 months	NS	HbA1c reduced (P = 0.03). Greater reduction with the LCD (p = 0.03)	TG reduced (P = 0.02). No difference between groups	NS	30 ± 13 E% CH 45 ± 9 E% fat 25 ± 7 E% protein
VERY LOW-CARBOHYDRATE DIETS											
Daly et al.,[32] UK (2006)	Randomized controlled trial	102 obese patients with poorly controlled type 2 diabetes	< 70 g/d CH (22 E%) No information provided on intake of fat and protein	45 E% CH[g] 33 E% fat[g] 21 E% protein[g]	Weight HbA1c TG SBP Compliance by food records and attrition	3 months	Greater reduction in weight with the LCD (P = 0.001)	No difference between groups	No difference between groups	No difference between groups	34 E% CH 40 E% fat 26 E% protein
Davis et al.,[37] USA (2009)	Randomized controlled trial	105 overweight type 2 diabetes patients	20–25 g/d CH (5–6 E%) for 2 weeks, then a 5 g increase each week	50 E% CH[g] 25 E% fat 19 E% protein[g]	Weight HbA1c1 LDL, HDL, TG, TC Blood pressure Compliance by food records and attrition	12 months	NS[f]	NS[f]	Greater increase in HDL with the LCD (P = 0.002).	NS[f]	33 ± 13 E% CH 44 ± 11 E% fat 23 ± 7 E% protein
Goldstein et al.,[40] Israel (2011)	Randomized controlled trial	56 obese type 2 diabetes patients	<25 g/d CH (<6 E%) for 6 weeks, then <40 g/d (<10 E%) No restrictions on intake of fat and protein	80 E% divided between CH and fats 10–20 E% protein	Weight HbA1c HDL, TG, TC Blood pressure Compliance by food records and attrition	12 months	Weight reduced (P < 0.001). No difference between groups	Reduction in HbA1c[f] No difference between groups	NS	NS	85 ± 35 g CH (20 E%) 111 ± 45 g fat (58 E%) 102 ± 37 g protein (24 E%)
Guldbrand et al.,[42] Sweden (2012)	Randomized controlled trial	61 type 2 diabetes patients	20 E% CH 50 E% fat 30 E% protein	55–60 E% CH 30 E% fat 10–15 E% protein	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	24 months	Weight reduced (P = 0.020 and 0.011). No difference between groups	NS	LDL and HDL improved (P = 0.020 and < 0.001). No difference between groups	SBP and DBP reduced (P = 0.012 and 0.004). No difference between groups	31 ± 6 E% CH 44 ± 5 E% fat 24 ± 4 E% protein
Jonasson et al.,[47] Sweden (2014)	Randomized controlled trial	61 type 2 diabetes patients	20 E% CH 50 E% fat 30 E% protein	55–60 CH 30 E% fat 10–15 E% protein	Weight[f], HbA1c LDL, HDL TG, TC Compliance by food records and attrition	6 months	Weight reduced[f] No difference between groups	HbA1c reduced (P < 0.01). No difference between groups	HDL increased (P < 0.05). No difference between groups	NA	25 ± 8 E% CH 49 ± 8 E% fat 23 ± 4 E% protein

(*Continues*)

TABLE 1 (Continued)

Study details	Study design	Participants randomized	LCD	Comparator	Outcome	Duration	Weight	HbA1c	Serum lipids	Blood pressure	Compliance with LCD presented as mean ± SD
Samaha et al.,[31] USA (2003)	Randomized controlled trial	52 severely obese type 2 diabetes patients	<30 g/d CH (8 E%) No restrictions on intake of fat	51 E% CH[g] 30 E% fat 16 E% protein[g]	HbA1c Compliance by food records[i]	6 months	NA	NS[f]	NA	NA	37 ± 18 E% CH 41 ± 16 E% fat 22 ± 9 E% protein
Shai et al.,[34] Israel (2008)	Randomized controlled trial	46 moderately obese type 2 diabetes patients	20 g/d CH (6 E%) for 2 months, then max 120 g/d (34 E%) No restrictions on intake of fat and protein	51 E% CH[g] 30 E% fat 19 E% protein[g] 50 E% CH[g] 35 E% fat 19 E% protein[g]	HbA1c Compliance by food records[i]	24 moths	NA	Hba1c reduced ($P < 0.05$). No difference between groups	NA	NA	40 ± 7 E% CH 39 ± 5 E% fat 22 ± 4 E% protein
Westman et al.,[35] USA (2008)	Randomized controlled trial	84 obese type 2 diabetes patients	< 20 g/d CH (5 E%) No information provided on intake of fat and protein	55 E% CH[g] 36 E% fat 20 E% protein[g]	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	6 months	Weight reduced ($P < 0.05$). Greater reduction in weight and BMI with the LCD ($P = 0.008$ and 0.05)	HbA1c reduced ($P = 0.009$). Greater reduction with the LCD ($P = 0.03$)	HDL and TG improved ($P < 0.05$). Greater increase in HDL with the LCD ($P < 0.001$)	SBP and DBP reduced ($P < 0.05$). No difference between groups	13 E% CH 59 E% fat 28 E% protein

Abbreviations: LCD, low-carbohydrate diet; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triacylglycerol; TC, total cholesterol; E%, percent of energy from macronutrient; CH, carbohydrate; NS, not significant; N/A, not assessed. Outcomes show significant findings within the low-carbohydrate group, and between dietary groups.

[a] Compliance measured at 3 months.
[b] *P* value represents between-group change from Week s12 to 64.
[c] Two control groups with the same macronutrient composition (American Diabetic Association (ADA) vs Traditional Mediterranean Diet (TMD).
[d] LCD significantly improved compared to ADA.
[e] LCD significantly improved compared to TM.
[f] *P* value on effect within diet group not provided.
[g] Macronutrient value shows actual intake during study/end of study.
[h] *P* value on effect between groups not provided, but authors state that no difference was seen between the two diets; no information available on within-group effect.
[i] Data on macronutrient intake during study was extracted from the entire study population.

intervention. Conversely, several trials permitted participants in the intervention to eat ad libitum while limiting carbohydrate intake.

Mean duration of diabetes among participants varied from 1 year to over 17 years and the participants frequently used medications, including insulin therapy,[30,31,34,35,37,41–45,47,49] anti-hypertensive drugs,[29,30,33,36,38,43,44,46] lipid lowering medications[29,30,33,36–38,42–44,46] and oral hypoglycaemic agents such as metformin,[30,31,35,37,38,42,46–49] sulfonylurea[27,30,31,37,38,42,46–49] and thiazolidinedione.[38,46,48,49] Dietary advice was provided by health professionals such as dietitians, nutritionists, diet counsellors,[29,31,33–37,39–47,49] physicians[42,47] and nurses[42] and involved both individual meetings and group sessions.

3.2 | Risk of bias in included studies

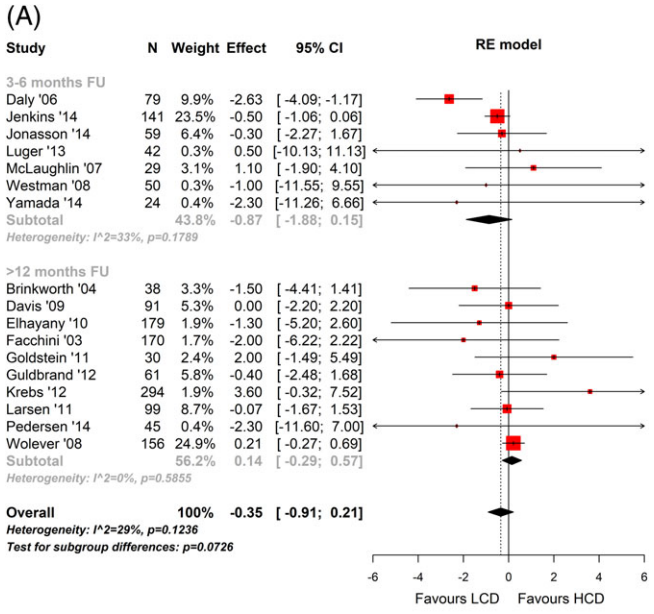
Assessment of risk of bias is summarized in Figure S1A and is shown for the individual studies in Figure S1B. Method of random sequence generation was reported and found to be adequate in 15 studies. Eight trials provided sufficient information concerning the proceedings of allocation concealment and they were rated as low risk. As expected, few studies blinded study participants and personnel to the dietary interventions, with the exception of one trial,[40] and were thus rated as unclear risk of bias. Five studies reported blinding of outcome assessors. One study [29] had a high risk of attrition bias as the result of incomplete reporting of outcome data, as only compliers were incorporated in the analysis and non-adhering participants were excluded. Selective reporting was found in four trials. Overall, when using the predefined criteria, the study level assessment showed that ten trials had a high risk of bias,[27–32,35,45,47,49] three had a low risk of bias[41,43,48] and the remaining ten studies were considered to have an unclear risk of bias.[33,34,36–40,42,44,46] (Figure S1). Funnel plots for the different outcomes did not indicate any publication bias (Figure S2).

3.3 | Body weight

Of the 20 studies that incorporated changes in body weight as an outcome, 17 provided sufficient information to be included in the meta-analysis and comprised 739 participants randomised to the LCD and 848 randomised to the HCD. Overall, an LCD was not associated with greater weight loss than an HCD in either short- or long-term studies (Figure 2A), but subgroup analysis suggested more positive results in short-term studies (≤6 months) than in studies with longer follow up (Table S3A). Sensitivity analysis showed less difference between LCDs and HCDs in studies with a low risk of bias than in studies with a high risk of bias (Table S3C). In the three cross-over studies of 3-month duration[28,29,38] that did not fulfill criteria for inclusion in the meta-analysis, one[38] showed greater weight loss associated with LCDs. The certainty of evidence was moderate, with little heterogeneity (I^2 = 29%) (Table S4).

3.4 | Glycaemic control

LCD was associated with greater overall reduction in HbA1c (MD, −1.0 mmol/mol; 95% CI, −1.9, −0.1 [−0.09%; 95%, CI −0.17, −0.01]) in the 16 studies included in the analysis. This result is largely driven by the results of the short-term studies (Figure 2B and Table S3A) and



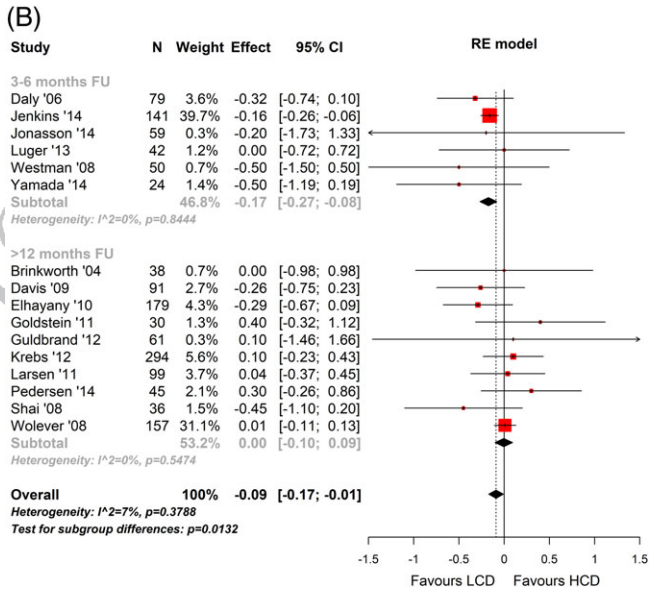


FIGURE 2 Meta-analysis of changes in A, body weight (kg) and B, HbA1c (%) divided according to study duration

by trials associated with a high risk of bias (Table S3C). Of the three short-term studies not included in the meta-analysis,[28,29,38] one[38] showed greater improvements with LCDs. The evidence was considered as having moderate certainty for this outcome (Table S4).

3.5 | Serum lipids and blood pressure

Sixteen RCTs are included in the pooled analysis of the effects on HDL-cholesterol and triglycerides, 15 studies in the analysis of LDL-cholesterol and 14 in the analysis of total cholesterol. The meta-analyses showed no significant difference between groups in effect on HDL-cholesterol (MD, 0.04 mmol/L; 95% CI, −0.01, 0.10; low evidence), on LDL-cholesterol (MD, −0.01 mmol/L; 95% CI, −0.13, 0.11; low evidence) and on total cholesterol (MD, 0.04 mmol/L; 95% CI, −0.12, 0.20; low evidence), but showed a slightly greater reduction in

triglycerides with an LCD (MD, −0.13; 95% CI, −0.24, −0.02 mmol/L; low evidence), (Figure 3D and Table S4). There was evidence of considerable between-study heterogeneity for triglycerides (I^2 = 57%; P < 0.003), for HDL-cholesterol (I^2 = 72%; P < 0.0001), for LDL-cholesterol (I^2 = 64%; P = 0.0004) and for total cholesterol (I^2 = 71%; P < 0.0001).

The reasons for the observed heterogeneity were explored in subgroup and sensitivity analyses. No consistent subgroup effects were observed across the three outcomes, although HDL-cholesterol was slightly higher with LCDs than with HCDs in long-term studies (P = 0.10) (Figure 3B and Table S3A) and LDL-cholesterol was higher in VLCD trials compared with moderate LCDs (P = 0.05) (Table S3B and Figure S3). Trials with low risk of bias showed less difference between LCDs and HCDs concerning changes in HDL-cholesterol and triglycerides than trials associated with high risk of bias, whereas the results were more consistent concerning LDL- and total cholesterol.

Sixteen trials examined the effect of an LCD on blood pressure. As shown in Figure 4A and B, the pooled effect from the meta-analysis indicated no significant difference in the effect of an LCD on systolic blood pressure (SBP) and diastolic blood pressure (DBP) when compared to control (SBP: MD, −0.93 mm Hg; 95% CI, −2.24, 0.37; DBP: MD, −0.21 mm Hg; 95% CI, −1.20, 0.79). Two of the three studies that were not included in the meta-analyses showed a greater reduction in DBP in the LCD group.[36,38] The certainty of evidence was considered low for both outcomes because of risk of bias and imprecision (Table S4). No evidence of between-study heterogeneity was identified in the meta-analyses (I^2 = 0%).

3.6 | Compliance and attrition rate

By using 24-hour recalls or food records, nine out of 18 studies found that dietary intake of carbohydrates in the LCD were 5 E% within what was recommended. In seven out of nine trials that observed low

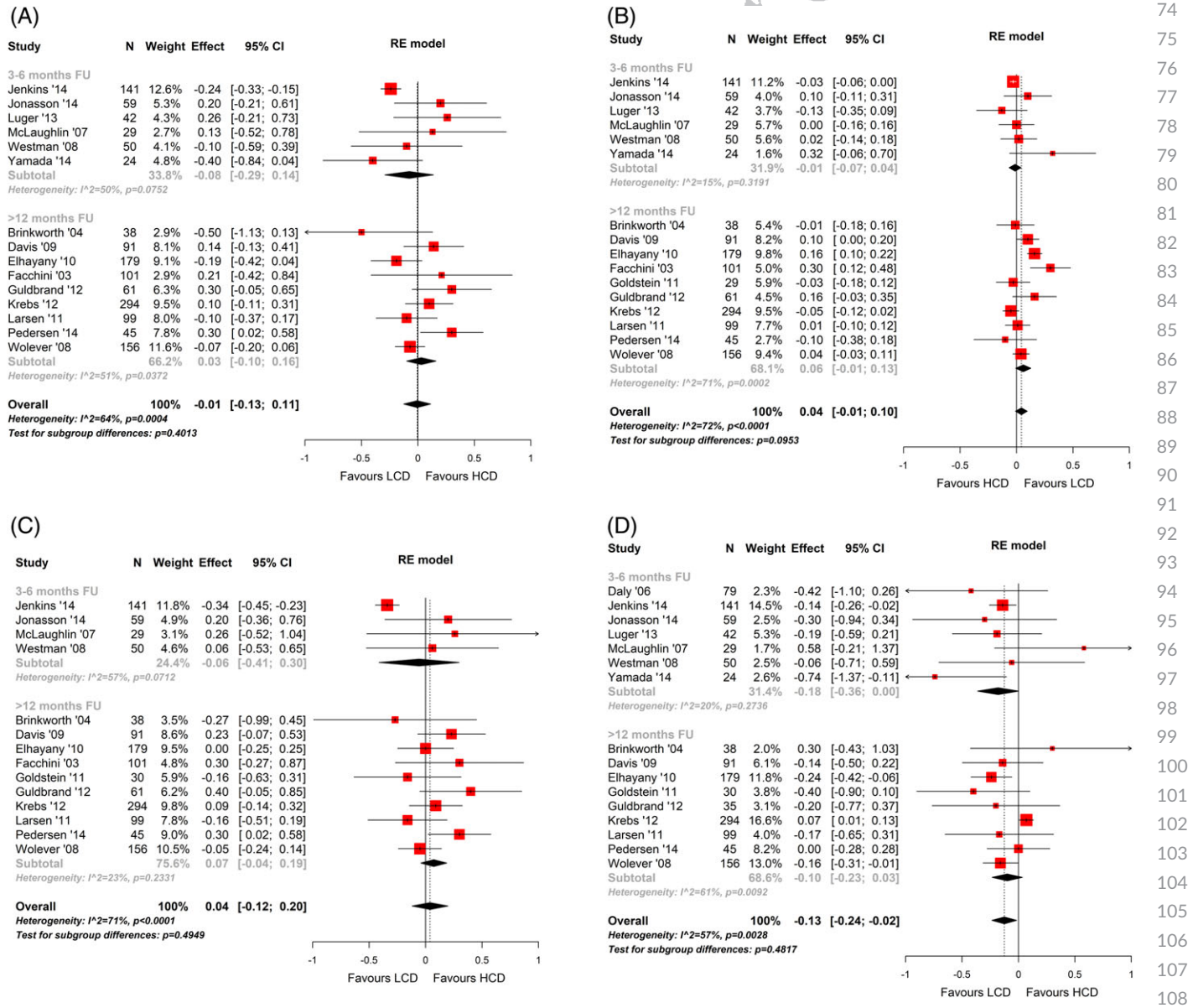


FIGURE 3 Meta-analysis of changes in A, LDL-cholesterol, B, HDL-cholesterol, C, total cholesterol and D, triacylglyserols, all measured in mmol/L, divided according to study duration

Color Figure – Print and Online

compliance, participants were receiving VLCDs with 5 E% to 22 E% from carbohydrates.[31,32,34,35,37,40,42] Four of these studies were based on an Atkins diet.[34,35,37,40] In the meta-analysis of attrition rates between LCD and HCD groups, no detectable difference in attrition was observed (RR, 1.08; 95% CI, 0.92, 1.27; I^2 = 0%) (Figure 4C). Results were similar in trials associated with high and low risk of bias. The certainty of evidence for attrition was downgraded to low because of risk of bias and imprecision (Table 4).

3.7 | Carbohydrate and fat quality in the diets

Seven of the included studies gave no information regarding dietary intake or gave only information concerning macronutrient distribution. Sixteen studies assessed dietary intake, 15 of which reported information regarding the nature of the carbohydrate (fibre, glycaemic index or load, sucrose, key foods provided in feeding trials). In nine of 15 trials the intake of fibre was higher in the HCD, while six trials reported no differences in fibre intake. Glycaemic index and glycaemic load were higher in the HCD in the two studies that reported this, while the intake of sucrose was lower in the LCD in one of the three trials that reported sucrose intake. In seven of the trials unsaturated fatty acids were substituted for carbohydrates in the LCDs, which resulted in a significantly higher intake of unsaturated fatty acids in the LCD compared with the HCD in six of the trials that reported fatty acid composition, while intake of saturated fat increased in only two of these studies.

4 | DISCUSSION

This systematic review and meta-analysis show that the minimally lower levels of HbA1c that are apparent when comparing diets with very low (21-70 g) or low (30 E%-40 E%) carbohydrate content with those providing a higher carbohydrate content (>40 E%) are driven by trials with a duration of 6 months or less and by trials associated with high risk of bias. The only consistent difference between the studies with higher and lower carbohydrate intakes was a small difference (0.13 mmol/L) in triglyceride levels, but this was most evident in trials with high risk of bias. No differences in weight, blood pressure or total, LDL- and HDL-cholesterol were apparent in either the relatively short- or long-term trials.

Our systematic review and meta-analysis identified all relevant trials published between 1983 and January 2016 and, therefore, includes an appreciably greater number of studies than earlier meta-analyses, enabling more convincing conclusions than previously possible. Other strengths included strict compliance with the established criteria for conduct of such a review and meta-analysis, including registration and specification of methodology prior to the literature search, the involvement of two researchers to independently extract and assess trials, and the use of GRADE methodology to evaluate the certainty of evidence. The inevitable limitation of any such review stems from the quality of the included trials and the extent to which participants adhered to prescribed diets, which inevitably diminishes over time in studies of individuals living in the community. The observation that trials with high risk of bias are associated with more

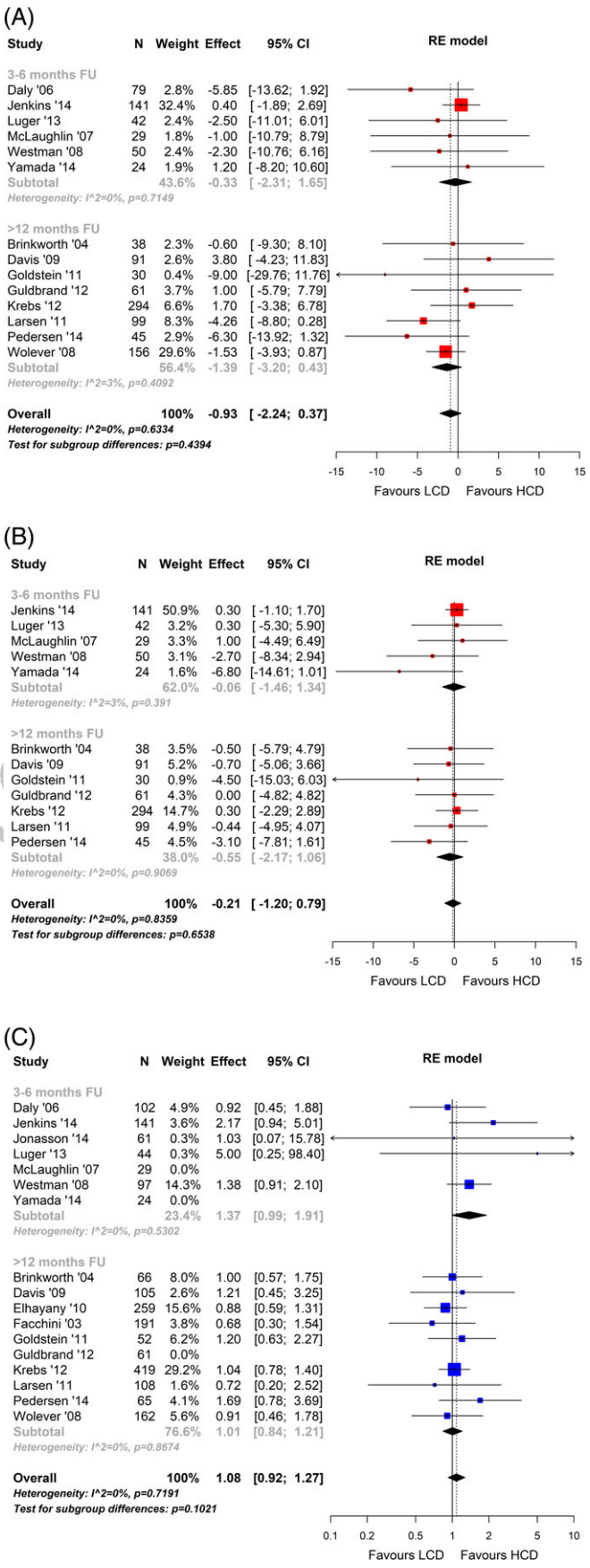


FIGURE 4 Meta-analysis of A, systolic and B, diastolic blood pressure (mm Hg) and C, attrition rate (risk ratio) divided according to study duration

favourable results for the LCD in many analyses highlights a potential pitfall in the interpretation of individual studies, meta-analyses and subgroup analyses. We attempted to assess compliance with prescribed diets and determine the extent to which the nature of carbohydrate might have influenced outcome. While there appeared to be a relatively high level of compliance with the LCD, it was evident that the ability to follow a diet with very low carbohydrate content was generally poor. Furthermore, changes in medications over time may have blurred the effects of differences in diet composition. The limited information given in the included studies suggests that, particularly in the VLCD groups, there was a greater reduction in the use of diabetes medication (mainly insulin) that may have masked a more positive impact on glycaemic control than what we have shown. On the other hand, only four studies showed a significant difference in change in diabetes medication between the diets; some of the studies repeated their analyses, adjusting for difference in medication and found that it did not alter the conclusions.

Ajala et al.[16] published a review and meta-analysis that examined the effects of low-carbohydrate, low-glycaemic index, high-fibre, high-protein, Mediterranean, vegetarian and vegan diets compared with control diets in trials that continued for 6 months or more. They reported a range of benefits, including an improvement in glycaemic control associated with all of these dietary patterns, and concluded that they were appropriate for individuals with diabetes. However, given that neither the low-carbohydrate nor the comparator diets were clearly defined, it is not possible to separate the effect of carbohydrate quantity from other aspects of the diet on the various outcome measures. Our meta-analysis also included trials with a range of carbohydrate intake, but differences between low and higher intakes were clearly specified and we used a random effects analysis, rather than a fixed effect analysis, as used by Ajala and colleagues,[16] to take into account the heterogeneity of studies. On the other hand, Naude et al.[20] concluded that altering carbohydrate quantity led to no difference in either body weight or glycaemic control; however, their meta-analysis included only five trials that involved isoenergetic comparisons, thus limiting the opportunity to find differences in weight change or glycaemic control as a consequence of altering macronutrient distribution.

In a more recently published systematic review and meta-analysis, Snorgaard et al.[21] concluded, as we did, that the modestly beneficial effect with respect to glycaemia conferred by LCDs was apparent only in the short term. However, our analysis differed from their approach in that we considered the outcomes of the relatively short- and long-term trials separately, whereas five of the eight studies providing data from a 3-6-month period in the review by Snorgaard et al. were also the source of data at 12 months. They also reported that the effect on glycaemic control was related to the extent of carbohydrate restriction. This association was totally dependent on the findings of two trials[50,51] with a duration of 3 months that were not included in our analyses because they involved participants with prediabetes[50] or an additional physical activity intervention.[51] When forest plots for VLCD diets and moderate LCD diets were examined separately, there appeared to be a better effect of VLCDs on HbA1c, also in our meta-analysis, but *post-hoc* subgroup analysis did not confirm this. On the contrary, the subgroup analysis showed that VLCDs had a less favourable effect on LDL-cholesterol compared with HCDs, while this difference was not shown in studies using moderate LCDs. The period covered in Snorgaard et al.'s review[21] (2004-2014) was appreciably shorter than that covered by the present study, and the upper cut-off used to define low-carbohydrate diets was 45 E%, whereas we chose the somewhat lower cut-off of 40 E%.

The short-term benefits of low- and very low-carbohydrate diets, in terms of weight loss and improvements in blood pressure and blood lipid profile, have also been shown in normoglycaemic individuals.[18,19] It has not been possible to determine whether the short-term improvement in glycaemic control and a range of cardiovascular risk factors is a consequence of weight loss or a direct result of carbohydrate restriction and/or the consequential redistribution of the proportion of energy provided by other macronutrients. It is also uncertain whether the failure to demonstrate meaningful long-term benefits results from failure to comply with advice to reduce carbohydrate intake or is a consequence of adaptation to an altered dietary pattern. Nevertheless, it is clearly the long-term outcome data that are relevant to the practical application of these findings.

Several issues must be taken into account when translating these findings into nutritional advice for individuals with type 2 diabetes. Weight reduction was a goal in the majority of the studies and the improvements seen with LCDs were observed mainly when weight loss was achieved. Thus, it is unclear whether the patient would benefit from carbohydrate reduction if weight loss is not achieved. Advice regarding the proportion of total energy provided by carbohydrate must also take into account the source and nature of carbohydrate and the effects of the other macronutrients. A substantial number of studies, carried out mainly in the 1980s and 1990s, demonstrated the benefit in terms of glycaemic control and cardiovascular risk factors associated with relatively high-carbohydrate diets that are rich in dietary fibre derived from legumes, vegetables and fruit.[4] Of particular relevance to interpretation of the results of the present analysis, triglyceride levels were not increased, even when carbohydrate intakes were high (~60 E%) in these earlier studies, provided that much of the carbohydrate was derived from sources rich in dietary fibre and slowly digested starches. Altered intakes of fat and protein, resulting from changes in the proportion of energy from carbohydrate, may also influence glycaemic control and the indicators of cardiovascular risk. Many of the LCD interventions included in our meta-analysis promoted increased intake of unsaturated fat, but not saturated fat. Thus, the findings have no direct bearing on several widely promoted low-carbohydrate high-fat diets in which saturated fat is not restricted or may even be encouraged. Detailed dietary data were not provided in many of the studies included in the meta-analysis; thus, it is not possible to distinguish among the effects of carbohydrate quantity and carbohydrate quality and other macronutrients. Finally, of the 13 studies that reported on the incidence of adverse effects, only one[30] reported a worse outcome concerning indicators of nephropathy with the HCD. The other trials reported no serious or important adverse events and no difference between groups in reported mild adverse effects such as mild hypoglycaemia.

Further long-term dietary intervention studies, taking into account both the amount and source of carbohydrate, would be helpful in refining nutritional recommendations for individuals with

diabetes. However, in practice, nutrition recommendations require translation into dietary patterns in order for them to be implemented. On the basis of currently available systematic reviews and meta-analyses there is an appreciable body of evidence to suggest that a traditional Mediterranean-type diet is particularly appropriate for individuals with T2DM.[16,52–54] Mediterranean diets vary in the proportion of energy provided by macronutrients, but are typically rich in pulses, fruits, vegetables and nuts, with olive oil being a major contributor to fat intake. Other dietary approaches, including a healthy Nordic diet and vegetarian diets, may also be beneficial for individuals with diabetes.[16,52,54–59] None of these dietary patterns is particularly low or high in carbohydrate. The range of possible diets allows personal preference to play a key role, while permitting appreciable restriction of rapidly digested starches and sugars in those with insulin resistance. While energy balance remains a cornerstone of all dietary advice for individuals with diabetes, the proportion of macronutrients seems to be less important.

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Conflict of interest

Author contributions

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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