Received: 1 June 2022 | Revised: 8 August 2022 | Accepted: 12 August 2022

DOI: 10.1111/dom.14837

ORIGINAL ARTICLE

WILEY

Very low carbohydrate (ketogenic) diets in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim: Very low carbohydrate/ketogenic diets (VLC/KDs) are popular but their role in managing pre-diabetes and type 2 diabetes (T2D) is uncertain. This study uses a systematic review and meta-analysis of randomized controlled trials to estimate the effect of these diets in this population.

Materials and Methods: A systematic review identified randomized controlled trials of at least 6 months duration comparing efficacy and safety of VLC/KDs (≤50 g carbohydrate or ≤10% total energy from carbohydrate per day) with a control diet (carbohydrate above the VLC/KD threshold) in adults with pre-diabetes or T2D. The primary outcome variable was glycated haemoglobin (HbA1c) after 12 months. The meta-analysis method was inverse variance weighting of mean values for continuous variables.

Results: Key word searches identified 2290 studies; 2221 were not in scope. A full text review of 69 studies identified eight meeting inclusion criteria; in total, it involved 606 participants. Six studies reported HbA1c (%) at 12 months; four as change from baseline with a fixed effects estimate (95% confidence interval): VLC/KD minus control of 0.01% (−0.22 to 0.25), $p = .91$; and two as change from baseline: −0.65% (−0.99; −0.31) [−7.1 mmol/mol (−10.8; −3.4)], $p < .001$. Serum triglycerides were lower with VLC/KD versus control: −0.28 mmol/L (−0.44 to −0.11), $p < .001$. High-density lipoprotein was higher with an estimate of 0.04 mmol/L (0.01 to 0.08), $p = .03$, in the five studies reporting 12-month summary data.

Conclusions: A VLC/KD may cause reductions in HbA1c and triglycerides in those with pre-diabetes or T2D but evidence of an advantage over other strategies is limited. More well-designed studies are required to provide certain evidence.

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

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1 | INTRODUCTION

The global prevalence of type 2 diabetes (T2D) has more than doubled since 1980[1] and now affects an estimated 537 million or 10.5% of adults aged 20-79 years.[2] Pre-diabetes, a state of glucose dysregulation that precedes the onset of T2D is common, with rates as high as 38% among adults in the United States.[3] Effective interventions may reduce significant comorbidities such as blindness, renal failure, peripheral neuropathy, cardiovascular disease (CVD) and depression.[4,5]

Obesity is the primary modifiable risk factor for pre-diabetes and T2D. A 5%-10% weight loss, through a reduced total energy intake, is an essential part of obesity management and the prevention and management of pre-diabetes and T2D.[6-8] However, there is no consensus as to a preferred dietary approach for weight loss, and sustained weight loss even over a moderate 12-month time period is difficult.[9,10] Furthermore, many dietary approaches focus on manipulating macronutrient proportions, which can have variable impacts on other cardiometabolic risk factors such as lipids.[8,11-14]

Ketogenic diets (KDs), typically referred to as 'keto' diets, have received significant media attention but their efficacy compared with other dietary approaches is uncertain.[15] A KD is characterized by very low carbohydrate (VLC) intake, typically <30-50 g daily, which can induce metabolism of protein and fat with subsequent production of ketone bodies. Experimental and non-experimental studies, and the popular press, report advantages of the 'keto' diet over other approaches to achieve weight loss, improve diabetes control by lessening insulin requirements and, in some cases, reverse diabetes.[16-18]

The efficacy of different dietary approaches for weight loss in obesity has been explored in several meta-analyses.[8,19,20] These meta-analyses are limited because studies using carbohydrate restricted diets across a broad range of carbohydrate intakes were combined. Although there have been meta-analyses of restricted carbohydrate intake diets,[14,21-24] none have specifically focused on glycaemic control, weight and CVD risk outcomes in people with pre-diabetes or T2D prescribed a VLC/KD. Therefore, the value of VLC/KD for weight loss, glycaemic control and CVD risk in these groups is uncertain.[13,14,25,26]

This study aimed to estimate the effect of VLC/KD compared with diets higher in carbohydrate, assessed by meta-analysis of randomized controlled trials (RCTs) in people with pre-diabetes or T2D, on glycated haemoglobin (HbA1c) and related metabolic variables.

2 | METHODS

This systematic review was conducted according to a registered protocol (PROSPERO ID CRD42021231935) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[27]

2.1 | Eligibility criteria

RCTs were included if they assessed the efficacy and safety of VLC/KDs (≤50 g carbohydrate or ≤10% total energy from carbohydrate per day) compared with a diet containing a carbohydrate content above this threshold among adults with pre-diabetes or T2D defined by any recognized international criteria. Studies needed to be of at least 6 months duration and report results at any of 3, 6, 12 and/or 24 months. Studies including the following participants were excluded: pregnant women including those with gestational diabetes, those aged <16 years and those with type 1 diabetes.

There were no restrictions regarding the minimum number of study participants. Studies including individuals with type 1 diabetes and/or obesity were included if separate data for patients with pre-diabetes or T2D were provided. Studies not published in English or published pre-2000 were excluded.

2.2 | Information sources

The following databases were searched from inception until 2 March 2021: Medline (OVID), Embase (OVID), Scopus, EBM Reviews—Cochrane Central Register of Controlled Trials (Ovid) and Web of Science. Reference lists from included studies were also searched for relevant studies.

2.3 | Search strategy

Search terms used were: (type 2 diabetes or diabetes mellitus or type two diabetes or T2DM or non-insulin dependent diabetes mellitus or NIDDM or late onset diabetes or adult onset diabetes or sugar diabetes or pre-diabetes or impaired fasting glucose or IFG or impaired glucose tolerance or IGT or impaired fasting glycaemia) AND (diet or carbohydrate-restricted or ketogenic diet or Atkins diet or keto or VLCK or very low cal* diet* or VLC* or very low carb*) AND (effect* or trial* or investigat* or random* or control* or experimental or compar* or matched or blind* or examine* or study or RCT*), using MESH terms where available. The complete search strategy for each database is shown in Supplementary File S1.

2.4 | Selection process

Two reviewers (AP-S and MW-M) independently screened titles and abstracts of all retrieved studies in Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) with disagreements resolved by consensus and with input from the wider research team where necessary. Reviewers then independently assessed the remaining studies based on the full text, and applying pre-specified eligibility criteria for included studies.

2.5 | Data collection process

Data extraction was done independently and in duplicate by the two reviewers using Covidence. The main paper and supplementary data were searched. If any relevant data were missing, study investigators were contacted by email with 1 month to respond with the requested data. A reminder email was sent after 3 weeks. Final data were confirmed by the study statistician (MW).

2.6 | Data items (outcomes)

Extracted data included: HbA1c, body weight, fasting glucose, fasting insulin, insulin sensitivity, body mass index, waist circumference, body composition, blood pressure, lipids [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TAG)], for each of the intervention and comparator groups.

2.7 | Study risk of bias assessment

Risk of bias was assessed by one reviewer and the study statistician (MW) using the Cochrane Risk of Bias Tool version 2 (RoB2) for randomized trials. This tool assesses random sequence generation, allocation concealment, blinding of participants, and personnel and blinding of outcome assessment. Each domain is assigned low, unclear or high risk of bias.

2.8 | Effect measures

The primary inferential outcome variable was HbA1c. The primary outcome time point was 12 months. All other continuous variables were treated as secondary outcome variables. Studies reported data summaries in one of two methods: (a) as change from baseline; or (b) summaries at specified time points for the VLC/KD diet and control diets. Where both the change from baseline and the summary data were reported, the summary was given priority. Because of the different analysis weights in relation to variance of change from baseline compared with endpoint only studies, typically smaller for change from baseline summary data, we chose to show separate analyses for those studies only reporting change from baseline summary data and those that only reported end of study summary data.

Data were converted to SI units except for HbA1c, which was reported in all studies as percentages. To do this, the following conversions were used: fasting glucose: mg/dl/18 to mmol/L, fasting insulin: micro IU/ml × 6 to pmol/L, waist circumference: inches × 2.54 to cm, cholesterols: mg/dl × 0.02586 to mmol/L and TAG: mg/dl × 0.01129 to mmol/L.

2.9 | Statistical analysis

The inverse variance method of meta-analysis was used to compare mean values between the treatment arms: ketogenic versus a comparison diet. Forest plots illustrate the effect sizes and Funnel plots explore publication bias. Heterogeneity was assessed by a χ^2 statistic and illustrated by the I^2 statistic and appropriate confidence interval (CI). Both fixed and random effects estimates are shown. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used.

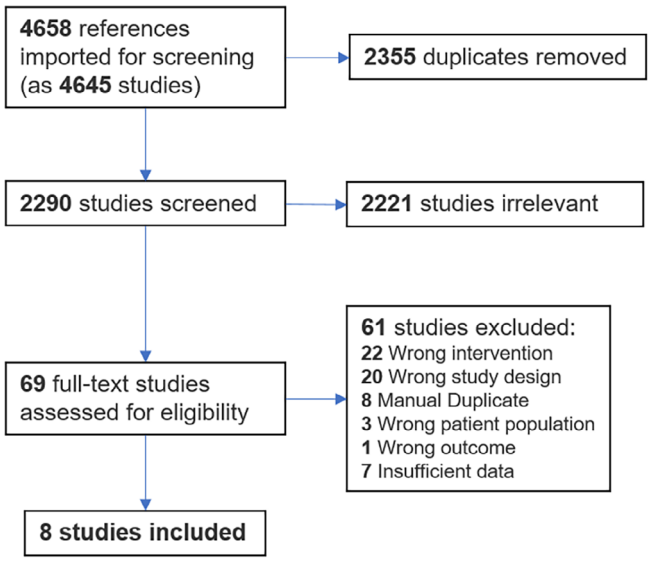

FIGURE 1 Flow chart of study selection

3 | RESULTS

3.1 | Study selection

Of 2290 identified studies, 2221 were not within the review scope based on abstract screening. Full text reviews were undertaken for 69 studies. Of these, eight studies published across 12 articles[28-39] met the inclusion criteria (Figure 1) involving 606 participants. The studies are summarized in Tables 1 and 2.

3.2 | Excluded studies

Six studies were not included in the meta-analysis (near misses). For three, the times of reporting data summaries did not fit the inclusion criteria of reporting at 3, 6 and/or 12 months.[40-42] A further two did not report sufficient detail on data summaries for the cohorts with T2D and the authors did not respond to requests for further data.[43,44] The sixth study had insufficient reporting of participant numbers in conjunction with reporting data summaries as 'Last Observation Carried Forwards', but without separate data summaries for completely observed participants. For this study, the corresponding author has since passed away.[45]

3.3 | Data extraction

For five studies, standard deviations needed to be extracted from CIs for between group differences, and from 'per-group' mean values.

TABLE 1 Demographics of included trials

Trial	Inclusion criteria	Prescribed insulin included or excluded	Baseline demographics: age (years), % male (intervention/ comparator if reported otherwise whole cohort)	Baseline outcome measures: HbA1c (%), weight (kg) (intervention/ comparator if reported otherwise whole cohort)	Intervention diet CHO	Comparator diet	Study duration	Adherence: CHO intake intervention/ comparator
Dyson et al. 2007, 2010 n = 26, 13 with T2DM. 22 (85%) completers Study funded by Abbott Laboratories	BMI >25 kg/m^2 With or without T2D	Excluded	54 years 30% male	7.3% 99 kg	≤40 g per day	Healthy eating advice + reduce TE intake by 500 kcal/ day	24 months	56.8/167.3 g at 3 months Blood ketones measured, LC group 0.1 vs. 0 at 3 months
Westman et al. 2008 n = 84; 50 (60%) completers Supported by Atkins foundation. Open access	T2D >1 year BMI 27-50 kg/m^2	Included	51.8 years 22% male	8.8/8.3% 108.4/105.2 kg	<20 g per day (given Atkins diet book)	Low GI reduced calorie diet (−500 kcal)	6 months	49/149 g at 2 years Urinary ketones: not reported
Davis et al. 2009 N = 105; 85 (81%) completers Supported by Atkins foundation. And others	T2D >6 months BMI ≥25 kg/m^2	Included	54/53 years 55/63% male	7.5/7.4% 93.6/101 kg	20-25 g CHO × 2 weeks then as lost weight increased by 5 g per week	Low fat diet (25% TE) no specified calorie restriction	12 months	6 months: 33.5/48.1% 12 months: 33.4/50.1%
Iqbal et al. 2010 n = 144; 68 (47%) completers Funded by VA merit review entry programme	T2D BMI ≥30 kg/m^2	Included	60 years 84.3/94.6% male	7.9/7.6% 118.3/115.5 kg	30 g per day with no fat or calorie restriction	Low fat diet (30% TE fat, <7% SAFA, <300 mg cholesterol, calorie deficit of 500 kcal/ day, fruit + vegetables)	24 months	Not reported
Goldstein et al. 2011 n = 52; 41 (79%) completers No funding reported	T2D BMI 30-39.9 kg/m^2 HbA1c >7%	Excluded	56 years 52% male	9.0/8.8% 91.7/92.2 kg	25 g CHO/day for 6 weeks increasing to 40 g daily No energy, protein or fat restrictions	Low fat calorie restricted ADA diet (10%-20% protein; 18%-20% MUFA, 8%-10% PUFA, 9%-10% SAFA; rest CHO with 35 g fibre)	12 months	3 months: 93/178 g 6 months: 93/190 g 12 months: 85/208 g 61% LC had urinary ketones at 6 weeks/3 months
Mayer et al. 2014 n = 46; 46 (100%) completers Funded by Department of Veterans Affairs	T2D BMI 27-30 kg/m^2 with obesity-related disease or >30 without	Included	56.6/54.7 years 86.4/87.5% male	7.6/7.6% 116.9/125.1 kg	≤20 g per day but not calorie restricted Increased if goal weight reached	Low fat diet + orlistat Restrict fat (<30% TE), SAFA (<10% TE), cholesterol (<300 mg) and calories (500-100 kcal deficit)	48 weeks	75.9/155.8 g at 48 weeks

TABLE 1 (Continued)

Trial	Inclusion criteria	Prescribed insulin included or excluded	Baseline demographics: age (years), % male (intervention/ comparator if reported otherwise whole cohort)	Baseline outcome measures: HbA1c (%), weight (kg) (intervention/ comparator if reported otherwise whole cohort)	Intervention diet CHO	Comparator diet	Study duration	Adherence: CHO intake intervention/ comparator
Tay et al. 2014, 2015, 2018 n = 115; 61 (53%) completers Funded by National Health and Medical Research Council	BMI 26-45 kg/m^2 T2D HbA1c ≥7%	Included	58 years 37/29% male	7.3/7.4% 101.7/101.6 kg	14% TE or <50 g per day calorie restricted (−30% TE)	Low fat, low GI, high carbohydrate (53%) diet (energy matched to intervention diet)	24 months	56.7/204.9 g at 24 weeks 74/217.6 g at 52 weeks 83/216 g at 24 months Plasma ketones: higher in LC group for 1 year
Saslow et al. 2014, 2017 n = 34; 29 (85%) completers Open access Funded by William K Bowes Jnr Foundation	T2D/pre-diabetes HbA1c >6% BMI ≥25 kg/m^2	Excluded (also >3 hypoglycaemic medications excluded)	64.8/55.1 years 43.7/11.1% male	6.6/6.9% 100.1/99.7 kg	≤50 g per day (20-50 g per day to achieve ketones)	Low fat, medium carbohydrate diet (45%-50% TE) calorie restricted diet (−500 kcal)	12 months	57.8/138.5 g at 3 months 44.1/160.7 g at 6 months 73.7/149.8 g at 12 months

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CHO, carbohydrate; GI, glycaemic index; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SAFA, saturated fat; T2D, type 2 diabetes; TE, total energy.

For another study, the standard deviation was extracted from a figure with mean values and error bars.[28,31-34,38] Some studies reported standard error of the mean, which was multiplied by the square root of the sample size to estimate a standard deviation. Where counts were not explicit for time points, the baseline count in the randomized groups was used. In one study, baseline data descriptions clearly had the mean and the standard deviation transposed.[31]

3.4 | Risk of bias in included studies

Risk of bias in studies was low overall, although some domains were high (Figure 2). Risk of bias from randomization and outcome measurement were both low. The high number of dropouts (up to 48% in one study) and missing data in some studies, and the number of secondary analyses in one study may have biased results.[32,33,38]

3.5 | Results of individual studies

The number of participants with pre-diabetes or T2D ranged from 13 to 144, and most were overweight or obese. Only one study included participants with pre-diabetes, and data summaries were combined with those with T2D.[35] Five studies included participants prescribed insulin. Intervention times ranged from 3 (with 3 months follow-up) to 24 months. All comparison interventions were low fat, mostly calorie reduced diets, and in two studies low glycaemic index foods were also encouraged. The mean age of participants ranged from 51 to 65 years. Studies differed in their approach to diabetes medication. Five included participants prescribed insulin and one allowed metformin only (Table 2). Seven studies encouraged physical activity in both groups, and no differences between groups were observed where measured (Table 2).

For the main outcome variable, HbA1c, two studies reported summaries rather than change from baseline and a pooled statistically significant difference between randomized arms after 12 months. This was an estimated difference of −0.65% (95% CI: −0.99; −0.31), $p < .001$ [−7.1 mmol/mol (−10.8; −3.4)] (Table 3, and Figure S1 in Supplementary File S2). For the four studies that reported HbA1c change from baseline, the pooled estimate was 0.01% (95% CI: −0.22; 0.25), $p = .91$ [0.11 mmol/mol (95% CI: −2.4; 2.7)] (Table 3, and Figure S2 in Supplementary File S2). In both analyses, there was no evidence of heterogeneity. In Supplementary File S2, Table S1 reports HbA1c outcomes at 3, 6 and 24 months.

Tables presenting weight, glucose, fasting insulin, Homeostatic Model of Assessment for Insulin Resistance (HOMA-IR), body mass index, waist circumference, fat free mass, fat mass, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL, HDL and TAG comparisons are in Supplementary File S2. Of the other variables assessed at 12 months, TAG was lower with a ketogenic compared with a control diet with an estimate of −0.28 mmol/L (95% CI: −0.44, −0.11; $p < .001$), and HDL was higher with an estimate of 0.04 mmol/L (95% CI: 0.01; 0.08; $p = .03$) in five studies. There were

TABLE 2 Exercise and medications

Trial	% Diabetes medication use intervention/ comparator	Were diabetes medications adjusted?	Antihyperlipidaemic medication use intervention/ comparator	Exercise advice given	Was exercise measured?	Was there a change or difference in exercise levels?
Dyson et al. 2007 and 2010 n = 26, 13 with T2D. 22 completers	Metformin only	No	Not reported	Both groups encouraged to exercise 30 min/ day, 5 days a week	No	NA
Westman et al. 2008 n = 84; 50 completers	75.9/95.2% taking diabetes medications including insulin	Yes, according to a pre-specified algorithm. 95.2% of intervention and 62.1% of comparator group reduced doses of diabetes medications	Not reported	Both groups encouraged to exercise 30 min/ day, 3 days a week	Yes: self report	No difference between groups
Davis et al. 2009 n = 105; 85 completers	Metformin: 78/86% Sulphonylurea: 44/52% Insulin: 35/24%	Thiazolidinediones discontinued and short acting insulin switched to glargine pre-trial. During study medications adjusted according to a pre-specified algorithm.	62/56%	Both groups recommended 150 min exercise/ week	No	NA
Iqbal et al. 2010 n = 144; 68 completers	Sulphonylurea: 57.1/43.2% Metformin: 61.4/52.7% Thiazolidine: 8.6/10.8%	No	45.7/62.2%	Both groups encouraged to exercise 30 min/ day, 5 days a week. Given a pedometer but no further advice	Yes: not specified	No difference between groups at any time point
Goldstein et al. 2011 n = 52; 41 completers	Not reported	Not reported	Not reported	Both groups encouraged to exercise 30 min/ day, 3 days a week	Yes: not specified	Both groups increased equally by 1 h/week

TABLE 2 (Continued)

Trial	% Diabetes medication use intervention/ comparator	Were diabetes medications adjusted?	Antihyperlipidaemic medication use intervention/ comparator	Exercise advice given	Was exercise measured?	Was there a change or difference in exercise levels?
Mayer et al. 2014 n = 46; 46 completers (full paper in Yancy et al. 2010)	Insulin ± oral agents: 31.8/33.3% Oral agents only: 54.6/58.3%	Yes, with an algorithm. MES was used in the analysis. MES decreased by −1.24 in the intervention vs. −0.82 $p = .27$	Not reported, but hyperlipidaemia reported: 63.6/75%	Both groups encouraged to exercise 30 min/ day, 3 days a week	Yes: Framingham index	No difference between groups
Tay et al. 2014, 2015, 2018 n = 115; 61 completers	Insulin: 10/11% Metformin: 79/72% Sulphonylureas: 34/28% Other: 9/11%	Yes, with an algorithm. MES was used in the analysis: At 12 months the intervention group had a greater reduction in MES ($p = .02$)	60/63%	Both groups 60-min exercise classes 3 times per week	Yes: class attendance records, 7 days accelerometry	At 12 months session attendance was similar between groups and activity counts had increased from baseline but no difference between groups
Saslow et al. 2017 n = 34; 29 completers	Metformin only: 31/44% Metformin + another agent: 44/28%	Medications adjusted by doctor based on BG monitoring	Not reported, but hyperlipidaemia reported: 81/56%	No specific advice given	Yes: IPAQ short form	No difference between groups

Abbreviations: BG, blood glucose; DM, diabetes; IPAQ, International Physical Activity Questionnaire; LC, low carbohydrate; LF, low fat; MES, medication effect score; T2D, type 2 diabetes.

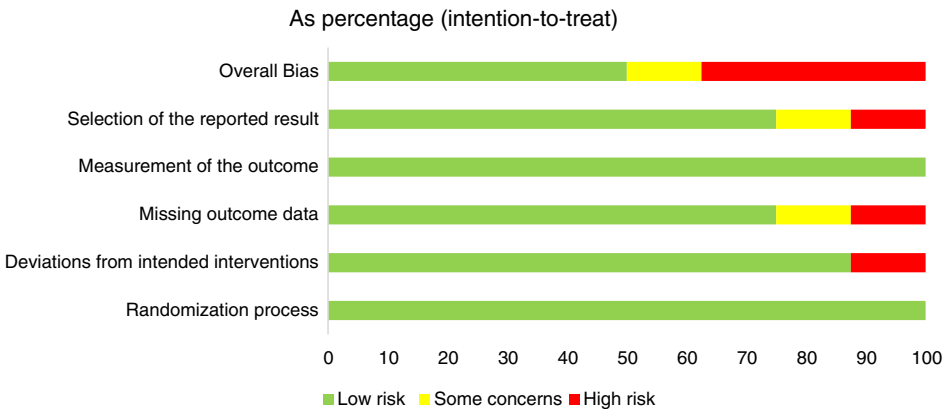

FIGURE 2 Risk of bias outcome

TABLE 3 Change in HbA1c (%)

	Mean ± SD			
	Active	Control	Difference (95% CI)	*p*
12 month change from baseline studies				
Davis 2009[a]	−0.02 ± 0.89 n = 47	0.24 ± 1.4 n = 44	−0.26 (−0.74; 0.22)	.29
Goldstein 2011[a]	1.5 ± 1.0 n = 14	1.1 ± 1.0 n = 16	0.40 (−0.32; 1.12)	.28
Iqbal 2010[a]	−0.1 ± 1.06 n = 28	−0.3 ± 1.26 n = 40	0.20 (−0.37; 0.77)	.50
Tay 2015	−1.0 ± 0.79 n = 41	−1.0 ± 0.75 n = 37	0.0 (−0.34; 0.34)	.99
Pooled				
Fixed effects			0.01 (−0.22; 0.25)	.91
Random effects			0.01 (−0.22; 0.25)	.91
Heterogeneity χ^2 (df)			2.78 (3)	.43
I^2 (95% CI)			0 (0; 83.5)	
12month studies reporting HbA1c summaries				
Mayer 2014	6.9 ± 1.03 n = 16	7.7 ± 1.10 n = 21	−0.8 (−1.50; −0.10)	.03
Saslow 2017[a]	6.1 ± 0.52 n = 14	6.7 ± 0.54 n = 15	−0.6 (−0.99; −0.21)	.005
Pooled				
Fixed effects			−0.65 (−0.99; −0.31)	<.001
Random effects			−0.65 (−0.99; −0.31)	<.001
Heterogeneity χ^2 (df)			0.24 (1)	.62
I^2 (95% CI)			0 (0 to NA)	

[a]SD calculated from confidence interval. Abbreviation: HbA1c, glycated haemoglobin.

no significant differences in any other variable. In comparisons of HbA1c and TAG, a negative value favours a VLC/KD and for HDL, a higher value favours a VLC/KD.

4 | DISCUSSION

Despite a great deal of public interest and popular press encouraging the use of VLC/KDs for weight management and improving metabolic health in the general population this systematic review and meta-analysis highlights that there is little evidence to support these claims for people with pre-diabetes or T2D. In total, 333 participants were involved in six studies with available data, and differences in reporting between studies with change from baseline versus absolute values did not allow pooling of all data. We found only one study meeting our inclusion criteria that included participants with pre-diabetes and data were not reported for them as a subgroup. Therefore, a separate analysis for those with pre-diabetes was not possible. Overall, it is difficult

to make firm conclusions from these data. Moreover, clinically important changes need to be considered over a period >12 months.

Nevertheless, this meta-analysis provides some evidence supporting a VLC/KD compared with diets higher in carbohydrate for lowering HbA1c and improving lipids in T2D. However, while there was a mean difference in HbA1c of 0.65% between diets in the two studies where HbA1c was reported at 12 months, in the four studies that reported change in HbA1c from baseline there was no difference between the KD and control diets at 12 months.

Two studies reported blood ketones with one study finding no significant difference in ketones[29] and the other showing higher ketone concentrations in the low carbohydrate (LC) group for the first year of the study.[37] Goldstein et al. measured urinary ketones and reported a higher level in the LC group at 6 weeks and 3 months.[31] It is possible that the lack of sustained difference in ketones suggests falling off of adherence to the VLC/KD, which may in part explain the limited effect on HbA1c.

The greater reduction in TAG of −0.28 mmol/L in pooled studies reporting change from baseline, and a difference of −0.17 mmol/L in those reporting absolute values at 12 months, is also small but clinically important. However, the difference in HDL is clinically insignificant, and there was no effect on LDL. Taken together, these data provide some supporting evidence that VLC/KDs in those with pre-diabetes or T2D may improve serum lipids, which were at least no different to diets higher in carbohydrate. Most importantly, VLC/KDs did not appear to worsen lipid profiles, a concern previously expressed because of a higher saturated fat intake.[47] In studies reporting the use of lipid-lowering medication[28,32,36] over 50% of participants were prescribed lipid-lowering agents, significantly influencing whether an effect of diet on lipids was observed. In the remainder of the studies, it is unknown whether participants were taking lipid-lowering medication.[29,31,33,35,38] However, overall total cholesterol and TAG values at baseline were lower than might be expected in those with T2D and obesity, which probably reflects the impact of lipid-lowering medication. There was no evidence that a KD was better than alternative diets in achieving weight loss, improving body composition or reducing blood pressure after 12 months.

Conducting and interpreting a meta-analysis of dietary intervention studies requires a detailed assessment of the diet and the outcomes of interest. Complex interactions between the dietary change and the outcomes; body weight, HbA1c, blood pressure or lipid profile, affect the interpretation and comparisons between different dietary approaches. Important variables include the type and proportion of macronutrients manipulated, amount of prescribed energy restriction, choice of control diet and energy matching, variability of tools used to assess intake, and fidelity of interventions. Other confounding factors such as level of support, exercise prescriptions and change in medications are associated with outcome measures.[23] In addition to the actual nutritional composition, the ability to sustain a particular diet is critical when considering the effectiveness of dietary interventions, with multiple factors such as convenience, health literacy, self-discipline, stress, family and social support, socioeconomic deprivation, cultural factors, and wider obesogenic environmental factors, such as food advertising, influencing outcomes.[46,47]

These complexities are illustrated in Tables 1 and 2. In this systematic review and meta-analysis, the comparator diet in most studies contained low fat intake (25%-30% total energy)[28,31-33,35,36] and most but not all prescribed a calculated total energy deficit.[29,31-33,38] However, the study by Tay et al. was an exception. In this study energy intake was matched with the ketogenic group,[36] which would make it very unlikely to see any difference in weight or body composition between groups. Three studies focused more on total protein content or specific dietary components such as fibre, monounsaturated or polyunsaturated fats,[31-33] all of which have effects independent of total carbohydrate intake on glucose metabolism and lipids.

There were also important differences within the VLC/KD intervention between studies. For example, some studies addressed the potentially negative impact of increases in saturated fat on lipids and glucose metabolism by specifically promoting monounsaturated and polyunsaturated fat over saturated fat[29,31,32,36] and others did not.[28,33,35,38]

The degree of carbohydrate restriction appears to be a relevant factor when considering the extent of HbA1c reduction compared with control diets in people with T2D as shown in a recent meta-analysis of studies with a wider range of carbohydrate restriction.[23] However, Gram-Kampmann et al.[48] emphasized in their study of moderate carbohydrate restriction in T2D, which showed a −7.5 (1.8) mmol/mol [−0.7% (0.2)] greater reduction in HbA1c compared with a low fat control diet that such variation in effect size is influenced by any associated energy restriction in combination with any medication changes. With these caveats in mind, it appears that with greater carbohydrate restriction, there are greater benefits for glycaemic control.

In general behavioural terms and specifically in dietary modification, the more restriction the likelihood of long-term adherence is lower.[49,50] Therefore, while the studies reported in this and other meta-analyses[26,51] broadly show greater improvements in glycaemic control and sometimes weight and lipids with VLC/KDs, studies are generally limited to 6 or 12 months, dropout rates in the ketogenic group can be as high as 54%,[32] and reported carbohydrate intake is often greater than what would constitute a KD by the end of the study (Table 1). Dansinger et al. have previously shown that weight loss is more related to adherence to a diet than to the actual dietary composition, and in their 12-month study the VLC/KD had the lowest adherence.[52]

No significant adverse events were reported in the two studies that reported this,[37] and Westman et al. indicated minor adverse effects of headache, constipation, diarrhoea, insomnia and back pain were reported in both diet groups.[38]

Other important variations between studies, which may influence the interpretation of this meta-analysis, include medication use and adjustment, and physical activity prescription and/or measurement. The inclusion of participants using different types of glucose-lowering medication and their adjustment varied across the studies. Four studies[28,33,36,38] included participants prescribed insulin, while one[29] only allowed metformin use and one[31] did not report prescribed medications. Two studies[29,32] did not allow medication adjustment during

the trial, and the others used pre-specified algorithms.[28,33,36,38] Two studies incorporated changes in medication use in their analysis.[33,36] Glucose-lowering medications and dose adjustments have a major modifying effect on our primary outcome measure (HbA1c) and this might overwhelm any real difference between dietary interventions.

Physical activity also has an important modifying effect on HbA1c and weight. Physical activity and changes in activity were variably reported and variably considered in studies included in this meta-analysis. Specific physical activity advice was given in all but one study[35] and was the same for both study groups. Where reported, no difference was observed in physical activity between groups,[31-33,35,36,38] and overall, it seems improbable that physical activity confounded interpretation of the effect of a VLC/KD on our outcomes of interest than medication use and adjustment.

This study has several limitations. Risk of bias in this cohort of studies was low. The studies that scored a higher risk mainly did so because of high participant dropout numbers. There are some statistical analysis limitations. It is difficult to reconcile that the studies that reported mean HbA1c gave a different estimate from those reporting change from baseline; however, the confounding factors discussed above may be relevant. Because multiple comparisons have been made, type I error inflation through repeated statistical testing may also be important. There was little overall evidence of heterogeneity although a limited number of studies contributed data for many outcome time points. For comparisons with no or few studies contributing data there may still be type 2 errors with wide CIs incorporating clinically important differences. Finally, the inability to access necessary data from two studies that met inclusion criteria, may have skewed the outcomes of our meta-analysis, although even if included the total number of participants would still have been very low and not included people with pre-diabetes.

5 | CONCLUSION

This systematic review and meta-analysis of the effect of VLC/KDs, compared with diets with higher carbohydrate content on glycaemic control, lipids and weight in people with pre-diabetes or T2D identified some evidence of an improvement in HbA1c and lipids. However, there are only a small number of published RCTs in this population group, with very limited data in pre-diabetes, and studies were generally short in duration. From the studies available there is no evidence of harm out to 12 months. However, the limited evidence does not identify whether there is a greater advantage to adopting a VLC/KD compared with other strategies. More well-designed studies, taking into consideration energy intake, more detailed assessment of nutrient quality, medication adjustments and physical activity levels, with outcomes at ≥24 months are required to provide more certain evidence of benefit or harm.

ACKNOWLEDGMENTS

Otago University Wellington Reference Librarians for assistance with searching. Open access publishing facilitated by University of Otago, as part of the Wiley - University of Otago agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data are included in the supplementary file.

REGISTRATION

PROSPERO International prospective register of systematic reviews PROSPERO ID CRD42021231935 Under the title: 'Ketogenic diets in pre-diabetes and type 2 diabetes: a systematic review and meta-analysis'.

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SUPPORTING INFORMATION

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

How to cite this article: Parry-Strong A, Wright-McNaughton M, Weatherall M, et al. Very low carbohydrate (ketogenic) diets in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2022;24(12):2431-2442. doi:10.1111/dom.14837