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An evidence-based approach to developing low-carbohydrate diets for type 2 diabetes management: A systematic review of interventions and methods

Jessica Turton MND[1] | Grant D. Brinkworth PhD[2] | Rowena Field MPhty[1] | Helen Parker PhD[1,3] | Kieron Rooney PhD[1,3]

[1]Faculty of Health Sciences, Discipline of Exercise and Sport Science, University of Sydney, Sydney, New South Wales, Australia

[2]CSIRO – Health and Biosecurity, North Ryde, New South Wales, Australia

[3]Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia

Correspondence
Dr Kieron Rooney, PhD, Discipline of Exercise and Sport Science, Faculty of Health Sciences, University of Sydney, 75 East Street, Lidcombe, New South Wales 2141, Australia.
Email: kieron.rooney@sydney.edu.au

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Abstract

Aim: To identify core diet and delivery components of low-carbohydrate (CHO) diets that have demonstrated efficacy for type 2 diabetes (T2D) management.

Materials and methods: MEDLINE, Pre-MEDLINE, EMBASE, CINAHL and the Cochrane Library of Controlled Trials databases were systematically searched from inception until August 18, 2018. Primary intervention studies of low-CHO diets (≤130 g/d or 26% total energy intake [TEI]) were included. Content analysis was performed on the low-CHO diet protocols classified as safe and effective for T2D management.

Results: A total of 41 studies published between 1963 and 2018 were included, of which 40 were classified as safe and effective for inclusion in the primary analysis. Thirteen studies (13/40) were on very-low-CHO diets (<50 g/d), 14/40 included low-CHO diets (≤130 g/d or 26% TEI), and 13/40 were adapted according to participant progress. Thirty-one studies reported a total energy prescription, of which 18/31 encouraged ad libitum intakes. Twenty studies reported a prescribed dietary fat amount, of which 18/20 were unrestricted or high-fat (>35% TEI). Twenty-six studies reported a prescribed dietary protein amount, of which 22 were unrestricted or were high-protein (>25% TEI). The types of dietary CHO, fat and protein recommended were predominantly whole foods. Common delivery methods reported were dietician and/or physician involvement, moderate to high frequency of contact (≥1 session/month) and use of participant self-monitoring.

Conclusions: Multiple approaches for developing and delivering a low-CHO diet intervention for T2D management are safe and effective. A comprehensive set of core dietary components to consider in the formulation of low-CHO diet protocols were identified for use in clinical practice and to inform evidence-based guidelines for T2D management.

KEYWORDS

carbohydrate restriction, clinical practice, diet intervention, dietary guidelines, low-carbohydrate diets, systematic review, type 2 diabetes

1 | INTRODUCTION

A growing body of evidence demonstrates that low-carbohydrate (CHO) diets are an effective dietary intervention for type 2 diabetes (T2D) management and have recently been acknowledged in public health guidelines of leading health authorities as a therapeutic treatment option.[1-3] Systematic reviews in T2D have consistently shown that, compared with traditional high-CHO diets, low-CHO diets achieve greater reductions in glycated haemoglobin (HbA1c) and antidiabetic drug use,[4,7] and more favourable changes in blood lipid profile with greater increases in HDL cholesterol and decreases in triglyceride levels.[5] Moreover, the HbA1c-lowering effects were greater when the level of dietary CHO prescribed was <26% total energy intake (TEI).[6,7] Despite strong clinical evidence and support for the use of low-CHO diets, there remains an absence of evidence-based practice guidelines to inform the development of safe and effective low-CHO diet protocols.

Previous systematic reviews have grouped all low-CHO diets together for statistical comparison versus traditional higher-CHO diets. To date, no systematic review exists investigating the different formats and characteristics of the low-CHO diet protocols used to achieve the observed effects in studies of T2D. This has limited the practical capacity for health professionals to successfully implement low-CHO diets in clinical practice using a systematic evidence-based approach. Low-CHO diets have been previously defined as <130 g/d CHO or 26% TEI from CHO.[8,9] Even with consideration of this definition, which excludes moderately restricted CHO diets that are often misclassified as low-CHO diets (26%-45% TEI as CHO), there remains a substantial degree of variation in the available CHO prescriptions within this range (0-130 g/d or 0%-26% TEI). Similarly, consensus recommendations for types and amounts of dietary fat and protein within low-CHO diets have not been established. Confusion surrounding appropriate modes of delivery, including the level of support required to maintain this form of dietary intervention, might also pose barriers to the implementation of low-CHO diets in clinical practice. Currently, healthcare practitioners must rely on the limited translational capacity of individual studies to guide the design of low-CHO diet interventions. A systematic review investigating low-CHO diet methods is needed to better inform the clinical practice management of T2D.

The aim of the present systematic review was to perform a content analysis on safe and effective low-CHO diet interventions in order to describe core dietary and delivery principles that have demonstrated efficacy for T2D management. These principles can be applied by healthcare professionals in clinical practice, or by researchers in the development of clinical trial protocols investigating the feasibility of low-CHO diets in populations where effect has not yet been established and further research is a priority (eg, type 1 diabetes).

2 | RESEARCH DESIGN AND METHODS

This systematic review was conducted following a registered protocol (PROSPERO 2018 CRD42018108208; available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018108208) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines (Table S1).

2.1 | Data sources and searches

The following databases for health sciences were systematically searched from inception until August 18, 2018: MEDLINE; Pre-MEDLINE; EMBASE; CINAHL; and the Cochrane Library of Controlled Trials. Search terms combined the population with the intervention. The complete search strategy for MEDLINE is shown in Table S2. An adapted SIGN filter for human studies was applied[10] and searches were restricted to articles in the English language only. Citations and abstracts of all retrieved articles were downloaded into EndNote reference management software (Endnote X7.7.1, Thomson Reuters 2016). Reference lists of included studies were also hand-searched and field experts were consulted for any additional publications that may have been missed.

2.2 | Study selection

After removal of duplicates, two reviewers (J.T. and R.F.) independently screened titles and abstracts of all retrieved records for obvious exclusions. Reviewers then independently assessed the remaining papers based on full text, applying pre-specified eligibility criteria for included studies. Disagreements were resolved by consensus through adjudication with a third independent researcher (K.R.). Included study designs were primary research studies of interventions with adequate reporting of pre–post outcome data. Case series analyses and case reports were included if detailed methods were reported. Retrospective reports of individuals who followed self-administered diets and non-English-language studies were excluded.

Studies were required to measure quantitatively and report the effects of a low-CHO diet intervention, defined as ≤130 g/d or 26% TEI as CHO in adults with T2D. Studies that did not report a CHO prescription as either g/d or a percentage of TEI were assessed by a registered dietician and were only included if the low-CHO diet intervention was designed to induce nutritional ketosis via carbohydrate restriction (not TEI restriction) and/or contained sufficient detail on the foods recommended and restricted to indicate a prescribed CHO amount ≤ 130 g/d. For studies that reported a CHO prescription as both g/d and as a percentage of TEI but for which there was inconsistency in their eligibility, the following approach was used: interventions of ≤26% TEI as CHO but >130 g/d were included unless they were overfeeding studies; or interventions of ≤130 g/d but >26% TEI were not included because this type of intervention was considered to be a very low-calorie diet restricted in CHO by default and was outside the scope of the present review. Studies of multi-stage dietary interventions where one or more stages satisfied the eligibility criteria were included if the low-CHO diet stage(s) of the intervention was implemented for >50% of the total duration. The low-CHO diet had to be actively delivered for a minimum of 2 weeks. Follow-up reports

encompassing periods for which there was no evidence of active delivery were not included.

Studies investigating conditions commonly associated with a diagnosis of T2D (eg, obesity, hypertension, metabolic syndrome) were included if participants with T2D were analysed separately or the mean HbA1c of participants at baseline was consistent with the World Health Organization's diagnostic criteria for T2D (≥48 mmol/mol [6.5%]).[11] Studies investigating other conditions of insulin resistance (eg, polycystic ovarian syndrome, gestational diabetes) or in which the effects of the intervention were confounded by the presence of major unrelated illness (eg, cystic fibrosis, critical illness) were excluded.

Studies were required to report on the pre–post change in at least one clinical outcome for T2D management. Primary clinical outcomes were standard measures of glycaemic control including HbA1c, use of anti-diabetic drugs and fasting blood glucose. Secondary clinical outcomes were standard measures of cardiovascular disease risk, including waist circumference, body weight, fasting insulin, fasting triglycerides and fasting HDL cholesterol. For weight maintenance studies, body weight was excluded as an outcome for the present review.

2.3 | Data extraction and quality assessment

Data extraction was carried out by J.T. using a piloted data extraction form (Table S3). For studies investigating multiple interventions, data from all eligible intervention arms were extracted and reported as separate interventions. Details on the low-CHO diet interventions were extracted from the methods section of the original papers. Risk of bias was assessed using the 12-item "National Institute of Health Quality Assessment Tool for Before-After Studies with No Control Group".[12] Case reports were automatically assessed as having a high risk of bias. All risk-of-bias assessments were performed at the study level; however, when information was specifically related to outcome measures (eg, "blinding of outcome assessment"), judgment was made according to the primary outcome for determining effect, HbA1c. If HbA1c was not measured or reported, the next reported primary or secondary clinical outcome was used for the assessment.

2.4 | Data synthesis and analysis

To classify low-CHO diets with an overall measure of effect for T2D management, absolute mean and variance values for primary and secondary clinical outcomes for the low-CHO diet intervention group(s) at baseline and immediately post-intervention were recorded. Sample size, intervention duration and statistical significance (i.e. *P*-values) were also recorded. Low-CHO diet interventions were classified as having an "overall positive effect" if there was a net change in the positive (beneficial) direction for at least one primary clinical outcome and no net change(s) in the negative direction for any. Studies that did not report on any primary clinical outcome could not be classified as having an "overall positive effect" and were not included in the final dataset for analysis. Any study reporting a statistically or clinically significant change in the negative direction of any secondary clinical outcome and/or the occurrence of any severe adverse events directly correlated to the low-CHO diet were excluded from the content analysis.

Content analysis was performed on the core dietary and delivery components of effective low-CHO diet protocols,[13] including the prescribed amounts and types of dietary CHO, total energy, dietary protein and dietary fat. Reported details on the dietary delivery method(s) and any additional dietary information (eg, sodium, fluids) were also analysed.

3 | RESULTS

3.1 | Literature search results

The database search identified 14 580 individual publications that were screened by title and abstract (Figure 1). Six additional possibly relevant records were identified through searching reference lists of included studies and in consultation with field experts. A total of 188 full-text articles were assessed for eligibility. Studies were excluded for the following reasons: dietary intervention >26% TEI (n = 54), intervention duration <2 weeks (n = 6), no T2D subgroups analysed (n = 10), study design was not an intervention (n = 8), inadequate measurement and/or reporting of outcomes (n = 23), conference abstracts (n = 44), non-English-language (n = 1), and a duplicate that had been incorrectly cited (n = 1). A total of 41 studies were eligible and included in the present review. A full list of excluded studies with reasons is provided (Table S4).

3.2 | Study characteristics

Study characteristics are presented in Table S5. Publication year ranged from 1963 to 2018 and the total number of adults with T2D who undertook a low-CHO diet during this period and were analysed in the literature was n = 2135. The mean age of participants ranged from 38 to 65 years, with only 7/41 studies reporting a mean age < 50 years.[14-20] Sample size ranged from n = 1 to n = 1000, and the active intervention durations ranged from 14 days to 24 months. Eighteen studies were randomized controlled trials,[17,21-37] three were non-randomized controlled clinical trials,[15,38,39] 16 were single-arm intervention studies,[16,18-20,40-51] two were retrospective case series analyses,[14,52] and two were case reports.[53,54] Thirty-four studies[14-30,32-34,36-38,43-50,52-54] were conducted in an outpatient setting, four studies[35,40,42] were conducted in an inpatient setting or with inpatient components, two studies[31,51] used a fully online setting and one study offered participants a choice of an outpatient clinic setting or an online setting.[39] Eighteen studies provided the mean reported CHO intake of participants as an adherence measure (Table S6).

3.3 | Risk-of-bias assessments

Overall risk-of-bias classifications (low, moderate, high) for each included study are presented in Table S5 and results from the formal

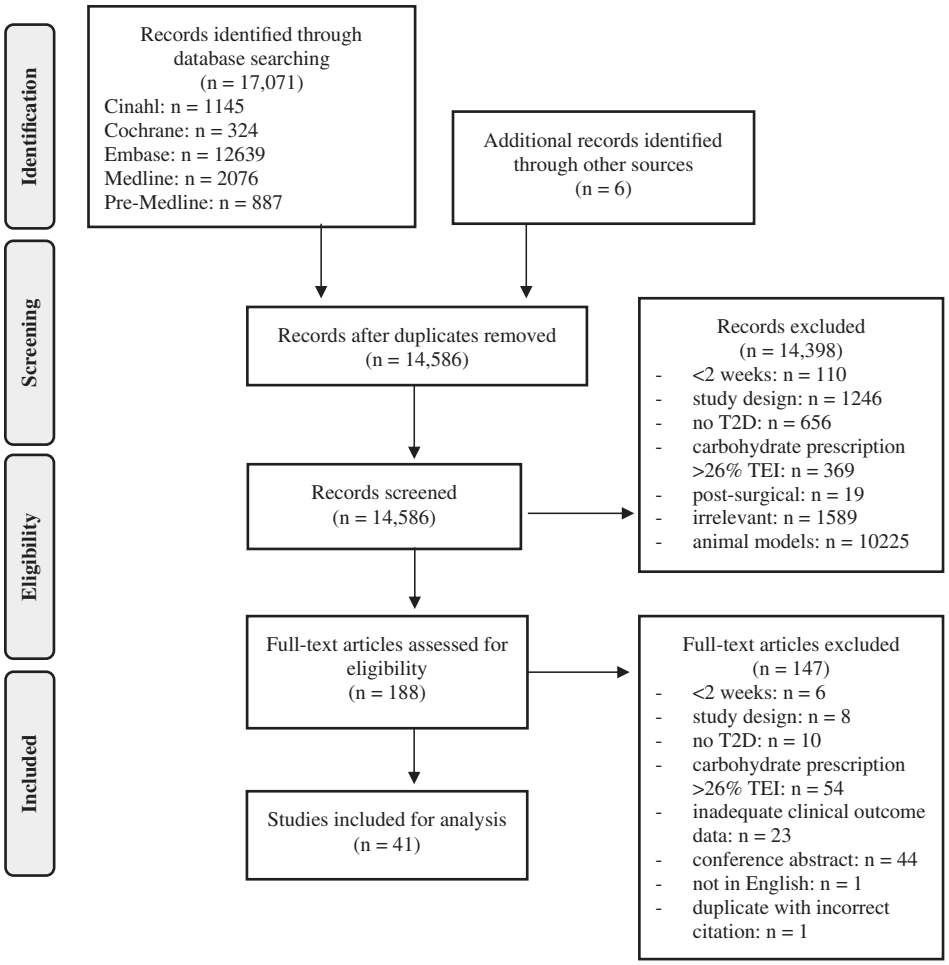

FIGURE 1 PRISMA flowchart. T2D, type 2 diabetes; TEI, total energy intake

risk-of-bias assessments are summarized in Figure S1. Eleven studies were considered to have a low risk of bias and 18 were considered to have a moderate risk of bias. Twelve studies were assessed as having a high risk of bias with predominant reasons including: study design (case report or retrospective chart review of only compliant participants); small sample size, coupled with no power calculations; lack of intention-to-treat analysis, coupled with low participant retention (<60%); and/or inadequate reporting of the methods of outcome measurement (for non-blood components).

3.4 | Overall effect classifications

Forty (40/41) included low-CHO diet interventions were classified as having an "overall positive effect" (Table S5). Thirty-four studies (34/41) reported a change in HbA1c after following a low-CHO diet, 33/41 reported a change in the use of anti-diabetic drugs, either in the methods as part of the intervention protocol (owing to the expectation of improved glucose control), or in the results (as an effect of the low-CHO diet; Table S7), and 23/41 studies reported a change in fasting blood glucose. Reporting of fasting blood glucose in one study[26] was unreliable and was excluded as an outcome to classify overall effect in the present review. In 1963, Silverstone and Lockhead[15] reported a mean reduction in weight after a low-CHO diet but no primary clinical outcomes of this review were reported so it could not be classified with an "overall positive effect" (referred to hereafter as "effective"). No study reported a statistically or clinically significant change in the negative direction for any secondary clinical outcome and no study reported severe adverse events that could be directly correlated to the onset of the low-CHO diet (Table S8).

3.5 | Content analysis of core dietary components

Forty studies (40/41) were included in the content analysis to describe the core components of effective low-CHO diet interventions. Table 1 presents the analysis of the dietary amount and type of prescriptions, and Table 2 presents the analysis of mode(s) of delivery and additional diet details.

3.5.1 | Dietary amount prescriptions

Forty studies (40/40) reported a dietary CHO amount (Table 1 and Table S5). Thirteen interventions (13/40) were very-low-CHO (defined as <50 g/d), of which 4/13 included a minimum CHO intake amount > 20 g/d, and 9/13 did not set any minimum amount. Fourteen interventions (14/40) were low-CHO (defined as ≤130 g/d or 26% TEI), of which 10/14 included a minimum CHO intake amount ≥ 50 g/d, and

TABLE 1 Content analysis of low-carbohydrate diet interventions for type 2 diabetes (dietary components)

	Frequency (*n*)	Bistrian 1976 [40]	Boden 2005 [41]	Daly 2006 [21]	Dashti 2007 [20]	Davis 2009 [22]	Dyson 2007 [23]	Feinman 2008 [53]	Fitz 1983 [42]	Friedman 2013 [43]	Gannon 2004 [24]	Goday 2016 [25]	Golay 1985 [44]	Goldstein 2011 [26]	Guldbrand 2012 [27]	Gumbiner 1998 [38]	Hallberg 2018 [39]	Hussain 2012 [19]	Iqbal 2010 [28]	Krebs 2013 [18]	Mayer 2014 [29]	Mueller 2011 [45]	Nielsen 2008 [46]	Nielsen 2006 [54]	O'Dea 1989 [47]	O'Neill 2003 [52]	Razak 2017 [17]	Rudnick 1965 [16]	Saslow 2017_1 [30]	Saslow 2017_2 [31]	Saslow 2018 [51]	Sato 2017 [32]	Stern 2004 [33]	Tay 2018 [34]	Unwin 2014 [49]	Unwin 2015 [50]	Vernon 2003 [14]	Von Bibra 2014 [35]	Westman 2008 [36]	Yamada 2014 [37]	Yancy 2005 [48]
Carbohydrate amount[a]	**40**	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Very-low-CHO (<50 g/d)	13	●	●		●		●	●		●				●					●			●				●	●					●					●	●		
- no minimum (0-50 g/d)	9	●			●		●	●		●				●												●					●						●		
- minimum (20-50 g/d)	4		●																●			●			●														
Low-CHO (≤130 g/d)	14			●							●				●								●	●	●			●		●	●		●	●	●		●		●	
- no minimum (≤130 g/d)	4																												●			●	●	●					
- minimum (50-130 g/d)	10			●							●				●								●	●	●			●			●						●		●	
Adaptive (individualized)	13					●			●			●	●			●	●	●		●	●								●	●										●
- body weight	9					●			●			●	●			●		●		●	●																			●
- blood ketones	3																●												●	●										
- glycaemic control	1																																			●				
- start very low (<50 g/d)	13					●			●			●	●			●	●	●		●	●								●	●							●			●
Total energy[b]	**31**	●	●					●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●
Ad libitum	18		●					●						●			●	●	●	●	●	●					●		●	●			●		●	●		●	●	●
Moderately restricted	6														●								●	●				●					●				●			
Severely restricted	2	●								●																														
Adaptive/variable	5										●	●	●			●									●															
Fat amount	**20**		●					●	●		●			●	●	●	●	●	●	●			●	●	●			●				●	●				●	●		●
Unrestricted	9		●					●						●			●	●	●													●						●		●
High-fat (>35% TEI)	9										●				●	●				●			●	●				●					●				●			
Low-fat (<20% TEI)	2								●																●															
Protein amount[c]	**26**	●	●		●			●	●	●	●	●	●	●	●	●	●	●		●			●	●	●			●				●	●	●	●		●	●		●
Unrestricted	10		●					●						●				●		●														●	●				●		●
High-protein (>25% TEI)	12	●							●	●	●		●		●		●						●	●	●								●				●			
Moderate-protein	4				●							●				●												●												
Carbohydrate type	**24**		●	●	●		●	●		●		●	●				●	●					●	●	●		●			●	●	●	●	●	●	●	●	●		●
Mostly whole foods	24		●	●	●		●	●		●		●	●				●	●					●	●	●		●			●	●	●	●	●	●	●	●			●
Include vegetables	23		●	●	●		●	●		●		●	●				●	●					●	●	●		●			●	●	●	●	●	●	●	●			●
Fat type	**21**		●	●	●		●	●			●	●	●	●		●	●		●											●	●		●	●	●	●	●	●		●

(Continues)

TABLE 1 (Continued)

	Frequency (n)	Bistrian 1976 [40]	Boden 2005 [41]	Daly 2006 [21]	Dashti 2007 [20]	Davis 2009 [22]	Dyson 2007 [23]	Feinman 2008 [53]	Fitz 1983 [42]	Friedman 2013 [43]	Gannon 2004 [24]	Goday 2016 [25]	Golay 1985 [44]	Goldstein 2011 [26]	Guldbrand 2012 [27]	Gumbiner 1998 [38]	Hallberg 2018 [39]	Hussain 2012 [19]	Iqbal 2010 [28]	Krebs 2013 [18]	Mayer 2014 [29]	Mueller 2011 [45]	Nielsen 2008 [46]	Nielsen 2006 [54]	O'Dea 1989 [47]	O'Neill 2003 [52]	Razak 2017 [17]	Rudnick 1965 [16]	Saslow 2017_1 [30]	Saslow 2017_2 [31]	Saslow 2018 [51]	Sato 2017 [32]	Stern 2004 [33]	Tay 2018 [34]	Unwin 2014 [49]	Unwin 2015 [50]	Vernon 2003 [14]	Von Bibra 2014 [35]	Westman 2008 [36]	Yamada 2014 [37]	Yancy 2005 [48]
SF reduced or min.	10			●			●				●	●		●		●			●												●			●						
SF not reduced or min.	11		●		●			●					●				●													●				●	●	●				●
Protein type	**19**	●	●	●	●		●	●		●		●	●	●		●		●							●									●						●
Mostly whole foods	16	●	●	●	●		●	●					●	●				●																●	●					
Include animal sources	16	●	●	●	●		●	●					●	●				●																●	●					
Use of supplements	3									●		●				●																								

Abbreviations: CHO, carbohydrate; min., minimised; n, sample size (number of studies); SF, dietary saturated fat; TEI, total energy intake.

[a]CHO amounts include no minimum (no minimum amount of CHO was set, such that an intake equivalent to 0 g/d was included in the prescription) and minimum (a minimum amount of CHO was set [eg, 21 g/d or 20-40 g/d]), such that an intake below the lower limit or single value was not recommended). Upper CHO limit for inclusion as a low-CHO diet study is ≤130 g/d or 26% TEI.

[b]Adaptive/variable energy prescriptions include studies that adapted or varied total energy according to individual progress or diet stage, including weight-maintaining studies wherein energy prescriptions were adjusted with a goal of maintaining body weight.

[c]High-protein prescriptions were defined as a protein amount > 25% TEI or > 1.2 g/kg ideal body weight per day. Moderate-protein prescriptions were defined as a protein amount of 15%-25% TEI or 0.8-1.2 g/kg ideal body weight per day.

4/14 did not set any minimum amount. Thirteen interventions (13/40) were adaptive (defined as prescriptions that adjusted according to individual participant progress), of which 9/13 were based on changes in body weight, 3/13 on blood ketones, and 1/13 on glycaemic control. Of these, all 13 studies set initial CHO amount to <50 g/d before increasing or decreasing CHO intake. For example, Hallberg et al[39] 2018 commenced participants on a CHO intake <30 g/d before personalizing the prescriptions according to the goal of achieving nutritional ketosis (beta hydroxybutyrate level of 0.5-3.0 mmol/L).

Thirty-one studies (31/40) reported a total energy prescription, of which 18/31 encouraged an ad libitum intake, 6/31 were moderately energy-restricted (defined as any set caloric prescription >800 kcal/d that was not weight-maintaining), 2/31 were severely energy-restricted (defined as any set caloric prescription ≤800 kcal/d), and 5/31 were adaptive (defined as any caloric prescription that was adjusted according to individual participant progress or diet stage; Table 1 and Table S5). For example, Goday et al[25] used a hypocaloric "active phase" (600-800 kcal/d) until adequate weight loss was achieved, then progressively increased CHO and energy during a "maintenance stage". Two other studies using adaptive energy prescriptions were weight-maintaining by design.[24,47] The moderately restricted energy prescriptions of the included studies ranged from 1357 to 2143 kcal/d, and the severely restricted prescriptions ranged from 300 to 800 kcal/d. One study did not set a quantifiable energy prescription and could not be categorized but incorporated "energy-balance principles" into participant education sessions.[21]

Twenty studies (20/40) reported a dietary fat amount prescription in their low-CHO diet protocols, of which 9/20 were unrestricted, 9/20 were high-fat (defined as >35% TEI) and 2/20 were low-fat (defined as <20% TEI; Table 1 and Table S5). The high-fat prescriptions of the included studies ranged from 45% to 75% TEI or 87 to 158 g/d as dietary fat, and the low-fat prescriptions ranged from 15% to 18% TEI.

Twenty-six studies (26/40) reported a dietary protein amount prescription, of which 10/26 were unrestricted, 12/26 were high-protein (defined as >25% TEI or > 1.2 g/kg ideal body weight [IBW] per day), and 4/26 moderate-protein (defined as 15%-25% TEI or 0.8-1.2 g/kg IBW per day; Table 1 and Table S5). The high-protein prescriptions of the included studies ranged from 28% to 65% TEI or 1.2 to 2.0 g/kg IBW per day, and the moderate-protein prescriptions ranged from 80 to 100 g/d or 0.8 to 1.2 g/kg IBW per day or were equivalent to 20% TEI. One study did not set a quantifiable protein prescription and could not be categorized but encouraged participants to consume their "usual protein intake".[30]

3.5.2 | Dietary type prescriptions

Twenty-four (24/40) studies reported on dietary CHO type in their low-CHO diet prescriptions (Table 1 and Table S5). Of these, all prescriptions included mostly whole-food sources of CHO (including vegetables, fruits, nuts, seeds, milk, yoghurt and wholegrains), with the specific inclusion of vegetables being highly common (23/24 studies). Three additional studies reported some information on the types of

TABLE 2 Content analysis of low-carbohydrate diets for type 2 diabetes (method of delivery and additional diet details)

	Frequency (*n*)	Bistrian 1976 [40]	Boden 2005 [41]	Daly 2006 [21]	Dashti 2007 [20]	Davis 2009 [22]	Dyson 2007 [23]	Feinman 2008 [53]	Fitz 1983 [42]	Friedman 2013 [43]	Gannon 2004 [24]	Goday 2016 [25]	Golay 1985 [44]	Goldstein 2011 [26]	Guldbrand 2012 [27]	Gumbiner 1998 [38]	Hallberg 2018 [39]	Hussain 2012 [19]	Iqbal 2010 [28]	Krebs 2013 [18]	Mayer 2014 [29]	Mueller 2011 [45]	Nielsen 2008 [46]	Nielsen 2006 [54]	O'Dea 1989 [47]	O'Neill 2003 [52]	Razak 2017 [17]	Rudnick 1965 [16]	Saslow 2017_1 [30]	Saslow 2017_2 [31]	Saslow 2018 [51]	Sato 2017 [32]	Stern 2004 [33]	Tay 2018 [34]	Unwin 2014 [49]	Unwin 2015 [50]	Vernon 2003 [14]	Von Bibra 2014 [35]	Westman 2008 [36]	Yamada 2014 [37]	Yancy 2005 [48]
Method of delivery	38	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Group sessions	14			●					●						●		●	●	●	●	●		●									●		●	●	●		●		●
Individual sessions	11			●					●			●						●	●							●							●	●	●	●				●
Dietitian involvement	14					●	●		●		●	●		●	●				●	●								●			●		●				●	●		
Physician involvement	10					●			●	●		●			●		●									●					●			●	●					
Frequency of contact	29	●		●		●		●	●	●	●	●		●	●	●	●	●	●	●		●	●				●		●	●	●	●	●	●	●	●		●	●	●
- high (≥2/month)	15	●						●	●	●	●	●		●		●	●	●		●										●						●		●		●
- moderate (≥1/month)	10			●															●				●				●		●		●	●	●	●					
- low (<1/month)	4					●									●							●																●	
Remote contact[a]	5											●					●								●				●	●									
Self-monitoring[b]	21					●			●					●	●		●	●	●	●		●	●		●	●			●	●	●	●		●	●	●			●	●
- glucose	12					●			●					●	●		●	●				●	●			●			●		●									●
- body weight	4																●													●				●	●				
- ketones	4								●								●												●	●									
- diet	12					●								●				●	●	●					●	●					●	●		●					●
- physical activity	2																		●							●													
Provision of food[c]	7		●							●	●					●									●								●			●			
Physical activity advice	15			●	●	●	●			●		●							●				●			●		●	●				●			●		●	●
Additional diet details	21	●		●	●			●	●	●		●	●	●		●	●	●		●			●				●			●				●	●	●		●		●
Fluid[d]	15	●						●	●	●				●		●	●	●									●			●				●	●	●		●		●
Sodium[e]	6	●		●				●									●																		●		●			
Micronutrient supp.	14	●			●				●	●		●	●			●	●	●		●			●												●		●		●

Abbreviations: supp., supplementation.

[a]Includes use of phone, email, video or web-based communication. Remote contact was either used in addition to in-person contact or for the majority/all contact.

[b]Self-monitoring of glucose and ketones was predominantly using the blood (but could also be urine). Self-monitoring of diet was periodic such as 3-day weighed food records at specified time-points for the purposes of calculating the reported dietary intake of participants during the study period or for the purposes of carbohydate-counting.

[c]Provision of all suitable meals, some meals and/or vouchers to subsidise key foods.

[d]Fluid recommendations include advice on water, broth, tea, coffee, other non-caloric beverages or alcohol. Milk was not considered a fluid in this review because it was considered under the carbohydrate prescription.

[e]Sodium recommendations include advice on salt, broth, bouillon stock or similar.

CHO foods recommended, but the information was insufficient to categorize robustly.[37,38,52]

Twenty-one (21/40) studies reported on dietary fat type in their low-CHO diet prescriptions (Table 1 and Table S5). Of these, 10/21 purposefully reduced or minimized the intake of saturated fat. Four studies reported their fat type prescriptions in a quantifiable manner ranging from 8% to 10%, 20% to 49%, and 10% to 13% TEI for saturated, monounsaturated, polyunsaturated fat, respectively.[24,34,35,38] One study was a liquid diet in which the fat was derived from monounsaturated-enriched sunflower oil.[38] Eleven studies (11/21) did not intentionally reduce or minimize saturated fat but recommended a variety of fat from whole food sources (including fatty cuts of meat, oily fish, full-fat cheese, cream, coconut oil, olive oil, nuts, seeds and avocado). One study specifically reported providing advice on adequate intakes of omega-3 and omega-6 polyunsaturated fats.[39]

Nineteen studies (19/40) reported on the types of dietary protein prescribed (Table 1 and Table S5). Sixteen (16/19) recommended the inclusion of mostly whole-food sources of protein (including meat, eggs, fish, cheese, milk, yoghurt, nuts and seeds). Sixteen (16/19) studies specifically reported the inclusion of animal proteins, yet no study (0/41) excluded animal proteins. Three studies (3/19) reported the complete or periodic utilization of protein preparations or supplements (defined as protein soups, powders, bars, shakes, smoothies or any protein derived from a laboratory) to substitute whole-food sources of protein.

3.5.3 | Method of delivery

Thirty-eight (38/40) studies reported use of common dietary delivery methods (Table 2 and Table S5). To provide dietary instruction, advice, education, reviews, support and other behavioural strategies (such as goal-setting), 14/40 reported the use of group sessions and 11/40 reported the use of individual sessions. It could be assumed that studies not specifically reporting the sole use of group sessions contacted participants on an individual basis, despite not reporting this detail. Fourteen (14/40) studies reported dietician involvement and 10/40 reported physician involvement. Twenty-nine (29/40) studies reported the scheduled frequency of contact with the research team and/or healthcare practitioners involved in the diet intervention delivery. Of these, 15/29 used high-frequency contact (defined as ≥2 sessions/month), 10/29 used moderate-frequency contact (defined as ≥1 session/month), and 4/29 used low-frequency contact (defined as <1 session/month). Five (5/40) studies reported the use of remote contact (eg, email, phone, web-based application, online discussion boards) for the majority or all of the scheduled contact,[31,39,51] or as a supplement to in-person contact.[25,39,52] One study offered participants a choice between remote and/or in-person contact.[39]

Twenty-one (21/40) studies reported the use of participant self-monitoring of glucose levels (12/21), body weight (4/21), ketones (4/21), diet (12/21) and activity levels (2/21). Of the studies recommending self-monitoring of diet, only three (3/12) reported use of CHO-counting.[22,28,33] Seven (7/40) studies reported provision of suitable foods for all or part of the low-CHO diet intervention. Fifteen studies (15/40) reported provision of physical activity advice or delivered a structured exercise intervention.

Twenty studies (21/40) reported additional diet information as part of their low-CHO diet protocols (Table 2; Table S5). Fifteen (15/40) reported fluid recommendations (relating to water, other non-caloric beverages, coffee, tea, broth and/or alcohol) and 6/40 reported sodium recommendations (relating to salt, broth, bouillon stock, etc.), of which 5/6 encouraged adequate, increased or ad libitum intake[14,36,39,40,53] and one recommended a restricted intake.[21] Fourteen studies (14/40) provided and/or prescribed micronutrient supplementation, of which multivitamins were common.[14,18,19,39,42,44,46,48]

4 | DISCUSSION

The present systematic review performed a content analysis of safe and effective low-CHO diet protocols published in primary studies of T2D management. This advances knowledge on the topic by describing a set of core components to guide the development of low-CHO diets in clinical practice or future research. All but one of the 41 included low-CHO diet interventions were classified as effective and none was found to be unsafe. This is consistent with previous systematic reviews and meta-analyses that have favoured low-CHO diets for improving glycaemic control and cardiovascular disease risk factors in T2D.[4-7] The present analysis determined that no one standard approach for developing low-CHO diet interventions targeting T2D exists and a range of approaches was identified. Nonetheless, the design of low-CHO diets can be simplified into the consideration of three primary components: the recommended or prescribed amount of CHO, the types of foods to be included, and the mode of delivery.

Previous systematic reviews have shown in T2D that CHO intakes of <45% TEI are superior to high-CHO intakes, and that low-CHO diets ≤26% TEI are associated with even greater reductions in HbA1c.[4-7] However, the optimal CHO prescription within this range (0%-26% TEI) remains unclear. The present review showed that low-CHO diets between 0 g/d[40,42] and 142 g/d (20% TEI)[24] are safe and effective. Many studies even included a range of available CHO intakes within a single prescription, commonly with no minimum CHO limit stipulated, such that all intakes between 0 g/d and the upper limit (eg, ≤25 g/d or < 130 g/d) were included (Table 1 and Table S5). It appears that no one single CHO amount for T2D is effective, yet there is growing interest in using more pronounced CHO restriction for at least part of the intervention duration. Very-low-CHO diet protocols (0-50 g/d) tended to be described as ketogenic diets[19,20,25,31,36,43] and/or set goals to achieve nutritional ketosis as measured by blood ketones.[30,31,39] Proposed benefits of nutritional ketosis for T2D include decreased circulating glucose and insulin[41] and increased ketone signalling, which may provide protection against oxidative stress.[55,56] More primary clinical trials directly comparing different CHO amounts within a low-CHO-diet context, including ketogenic diets, are required to better understand whether a specific CHO amount is optimal for T2D.

Nevertheless, two predominant strategies for setting a prescribed CHO amount were identified: fixed and adaptive. For fixed prescriptions, the recommended CHO amount remained (mostly) constant for all participants throughout the intervention (ie, minimal between-person or within-person variation). Some of the longest interventions (between 10 and 24 months) used this approach,[20,26,28,33,34,40,50,52,54] suggesting that the degree of CHO restriction required to improve T2D management should be (mostly) maintained; however, the actual necessity for patients to restrict CHO to a fixed amount long-term probably depends on the severity of their condition, including diabetes duration and remaining level of pancreatic β-cell function.[57] In addition, some patients might simply prefer a more flexible adaptive approach. The adaptive low-CHO diet interventions included in this review used a very-low-CHO prescription (<50 g/d) during an initial phase to adequately achieve individual participant progress, before adjusting the CHO amount, provided that progress was continued or maintained. The initial more restricted phase may be useful in promptly achieving targets for body weight, glycaemic control and/or nutritional ketosis to motivate patients to sustain behaviour change(s). A similar two-phase approach was used in a large-scale, multinational T2D prevention trial.[58] The prescription included a very-low-calorie diet (~800 kcal/d) during an initial weight-reduction phase to achieve >8% initial body weight loss before moving to a more flexible weight-maintenance phase.[58] Whether patients with T2D can return to a diet balanced in all three macronutrients after achieving outcome targets on a low-CHO diet requires further investigation in longer-term trials (>2 years).

It is well recognized that a dietary intervention is only effective if it is adhered to and sustained, and when developing low-CHO diets for use in clinical practice it is recommended that individual factors affecting adherence, such as socio-economic status and education level, are considered.[59] As a result of the incompleteness of reported CHO intake data (Table S6), definitive conclusions based on adherence in the included studies of this review were not drawn. Nevertheless, emerging evidence suggests that adherence to low-CHO diets may be greater with less restricted CHO intakes (15%-20% TEI) compared to severely restricted CHO intakes (5% TEI).[60] Notably, the two studies prescribing zero CHO intakes[40,42] were conducted >30 years ago where the food environment may have been more conducive to achieving and sustaining this type of low-CHO diet.[61]

Most low-CHO diet interventions prescribed ad libitum energy in combination with high or unrestricted amounts of fat and/or protein. Ad libitum energy prescriptions included those in which participants were encouraged to eat as much as they want, to eat to satiety or simply to not focus on the energy content of food at all. Given the strong associations between T2D and obesity,[62] cardiovascular disease[63,64] and renal disease,[65] it seems somewhat counterintuitive to develop a diet intervention that does *not* prescribe a specific energy level to achieve caloric deficit and avoid excessive fat and protein intakes. Nevertheless, the included ad libitum low-CHO diets produced a substantial average weight loss of −8.3 kg in people with T2D[17,18,26,28,31,39,41,45,49,53] and no diet negatively impacted cardiovascular risk factors, including HbA1c, blood lipids and waist circumference (Table S5). Although renal outcomes were not included in the present study, a recent systematic review showed no significant difference with regard to several measures of renal function between high-protein low-CHO diets and lower-protein high-CHO diets.[66] Plausible explanations include the reduction in appetite consistently demonstrated with low-CHO diets that promotes a lower caloric intake in the absence of a specific prescription,[67,68] and the "metabolic advantage" of low-CHO diets that has been shown to significantly increase total energy expenditure to further facilitate weight loss.[69]

Furthermore, the present findings suggest that the recommendation of specific food types might have a knock-on effect in regulating the amounts of dietary energy, protein or fat consumed on a low-CHO diet. The recommendation to include mostly whole foods was common amongst the included interventions. Although the definition of whole foods can vary, we defined whole foods as animal foods with minimal processing (eg, mechanical processing only) and plant foods that maintain their natural structural integrity. The degree of processing of plant foods in particular can significantly magnify the insulin response[70]; therefore, the common prescription to source CHO from vegetables in the low-CHO diet studies might have played an important role in regulating participants' energy intakes and improving glycaemic control. Most vegetables have a low digestible CHO content owing to their high proportions of water and fibre, and often displace the intake of highly processed CHO and discretionary foods.[71,72] Many of the included low-CHO protocols are ultimately in alignment with public health recommendations to consume a vegetable-rich diet for chronic disease prevention and management.[73-75]

Recommendations for the amount and type of dietary fat to consume remains a more heavily debated topic in T2D management. Traditional approaches for T2D promote low or reduced intakes of total and saturated fat while many of the low-CHO diets analysed in the present review recommended increased, high or unrestricted fat intakes. Discrepancy exists even within the low-CHO-diet studies between interventions that purposefully minimized or reduced saturated fat and those that did not. The effect(s) of dietary saturated fat on cardiovascular disease mortality and all-cause mortality remain inconclusive,[76] with some evidence suggesting reduced cardiovascular disease risk with low-CHO high-fat diets.[77-79] Regardless, the common prescription to include dietary fat from mostly whole-food sources might offer some natural protection against excessive intakes of any specific fatty acid. Many of the low-CHO diet foods that are recognized for their high saturated fat content also tend to contain a high, if not higher, monounsaturated fat content. For example, fat in whole eggs and beef rump is 43% and 45% monounsaturated and 36% and 45% saturated, respectively.[72] The cardio-protective effects of high monounsaturated fat intakes in T2D are well known,[80,81] yet greater primary research investigating the necessity to reduce saturated fat intake in the context of a low-CHO diet for T2D is required. The recommendation to include fat mostly from whole-food sources may sufficiently achieve balanced proportions of unsaturated and saturated fats without concern for rigid prescriptions.

The satiating effects of protein were also likely to promote self-regulation of dietary intake[82,83] and the common recommendation to include protein from mostly whole-food sources, especially animal proteins, may be uniquely successful for T2D management. Key nutrients obtained from consuming animal products include bioavailable protein, haem-iron, vitamin B12, zinc and long-chain omega-3 fats.[84] Low intakes of long-chain omega-3 fats have been linked to insulin resistance, while increased intakes have been shown to improve insulin sensitivity[85] and protect against cardiovascular diseases.[86] Vitamin B12 deficiency is common amongst individuals with T2D[87] with long-term metformin use proposed as a contributing factor.[88-90] Since B12 is essential for cardiovascular function,[91] diets low in animal foods may not be appropriate for T2D management. Nevertheless, the effects of low-CHO diets that exclude or limit animal proteins remain unclear and this is an area of research requiring further investigation.

Moreover, the intensive delivery structure used in most of the low-CHO diet studies is consistent with existing literature for enabling and sustaining effective lifestyle change. For example, the Diabetes Prevention Program Lifestyle Protocol included high frequency of contact and an extensive network of training, feedback and clinical support as key interventional aspects[92]; however, intensive practitioner involvement is not always feasible in clinical practice and use of remote contact (eg, email, phone, web-based) and automated delivery systems (eg, videos, podcasts) may be increasingly useful and warrant further research. Self-monitoring of outcomes such as glucose, body weight and ketones may also be prudent to promote self-accountability of behaviours,[93,94] particularly for interventions with less frequent practitioner interaction.

A key strength of the present review was the large amount of evidence and quality of the included studies, which were not limited to randomized controlled trials. This provides a high degree of confidence in the quality of evidence available to support and inform low-CHO diets in clinical practice. Content analysis of the low-CHO-diet protocols enabled synthesis and identification of the most frequent dietary components reported; however, it is important to acknowledge that this method has a high risk of reporting bias because the studies reported varying depths of detail about the dietary prescriptions and delivery method(s). The decision to include studies "from inception" meant that many authors could not be contacted for further details. In expectation of this, the primary analysis was limited to the data available from the published text. English-language-only studies were included because of time and resource constraints for translation from other languages, raising the possibility that information from non-English-language studies was missed.

As a result of the multi-factorial nature of the included interventions and the lack of consistency in the methodological details reported, it was not possible to perform meta-analyses comparing the effect(s) of the different design components. Nutrition researchers should consider the core dietary components described in the present review as the minimum level of detail required when reporting dietary protocols in the future. This review also lacked the scope to analyse comprehensively the additional diet details (eg, sodium) and the incorporation of physical activity. An interesting observation was that almost all studies reporting on sodium recommended adequate, increased or ad libitum intakes, which is in conflict with national public health recommendations.[75] Additionally, the benefits of physical activity for improving insulin sensitivity in adults with T2D have been analysed previously.[95] The variability in T2D populations (eg, age, sex, diabetes duration, comorbidities) across the included studies was also beyond the scope of the present analysis and should be considered in future reviews.

The present review advances the information from recent systematic research investigating low-CHO diets for T2D management and highlights a broad range of low-CHO diet interventions that are safe and effective. A comprehensive set of core dietary components to consider when developing low-CHO diets for use in T2D was identified that can inform clinical practice guidelines for the use of low-CHO diets in T2D management. These data may also contribute to the development of dietary protocols for future clinical trials investigating the feasibility of low-CHO diets in other clinical populations where effect has not been conclusively established.

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CONFLICT OF INTEREST

J.T. has given talks for "Low Carb Down Under" on her previous research and on the practical application of low-CHO diets and provides dietetic consultations from multiple clinical locations that support the use of low-CHO diets. K.R. has given talks for 'Low Carb Down Under' on the biochemistry of low-CHO diets and has been a collaborator on primary research investigating the effect of lower-CHO diets for weight loss. A full disclosure of previous funding and published research is available at http://sydney.edu.au/health-sciences/about/people/profiles/kieron.rooney.php.

No other author has any conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Author contributions to the paper were as follows: J.T.: conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the manuscript, primary responsibility for final content; G.B.: conception and design, analysis and interpretation of data, drafting and revising the manuscript; R.F.: acquisition of data; H.P.: analysis and interpretation of data, revising the manuscript; K.R.: conception and design, revising the manuscript, accountable for all aspects of the work. All authors read and approved the final manuscript.

DATA-SHARING

Data described in the manuscript, code book, and analytical code will be made available on request pending application and approval.

ORCID

Jessica Turton https://orcid.org/0000-0003-2263-9350
Grant D. Brinkworth https://orcid.org/0000-0001-9017-8395
Kieron Rooney https://orcid.org/0000-0001-6563-7617

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SUPPORTING INFORMATION

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

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