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Low Carbohydrate Diets for Diabetes: A Review of the Clinical Effectiveness and Guidelines

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Abbreviations

ADA	American Diabetes Association
BMI	body mass index
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
LDL	low-density lipoprotein
NMA	network meta-analysis
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
VA/DoD	Department of Veterans Affairs and the Department of Defense

Context and Policy Issues

Insulin is a hormone secreted by the pancreas and regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of carbohydrates.[1] Diabetes occurs when insulin is not produced enough or when insulin is not used effectively in human bodies.[2] Type 2 diabetes is associated with reduced insulin sensitivity[3] and accounts for more than 90% of the diabetes cases.[4] In 2017, It was estimated that 7.3% of Canadians aged 12 years and over were diagnosed with diabetes (type not specified) .[2] Aging and male sex are related to higher diabetes prevalence.[2] Diabetes is associated with a variety of long term complications, particularly heart disease, stroke, and kidney disease.[2] To prevent the progression of diabetes and the occurrence of complications, nutrition therapy has been found to be effective and several types of dietary interventions are promoted for patients with diabetes.[4] Dietary interventions are considered important for the fluctuations in blood glucose levels and improving the effectiveness of pharmaceutical interventions, such as insulin injection.[5] The restriction of carbohydrates can influence blood glucose levels and has been considered important for patients with diabetes.[4] There are various recommendations regarding the intake of carbohydrates in different guidelines.[4] A 2017 CADTH Summary of Abstracts report identified evidence to support the use of low-carbohydrate diets for obese patients with type 2 diabetes, compared with high-carbohydrate diets, low-fat diets, and other dietary interventions.[6] Low-carbohydrate diets were not compared with standard diets in this report.[6] There is a guideline by the Scottish Intercollegiate Guidelines Network (SIGN) identified in this report and low-carbohydrate diets are one of the dietary options for patients to manage diabetes.[6] Whether low-carbohydrate diets are superior to other diets is not explicitly stated in the guideline or in the report, particularly compared with standard diets or regular eating habits without restrictions by food groups. The SIGN guideline was also updated recently[7] and there are other guidelines available for patients with diabetes.[8] This report aims to review the evidence and clinical guidance regarding the use of low-carbohydrate diets among patients with type 2 diabetes.

Research Questions

1. What is the clinical effectiveness regarding the use of a low carbohydrate diet in adults with type 2 diabetes?
2. What are the evidence-based guidelines regarding the use of a low carbohydrate diet in adults with type 2 diabetes?

Key Findings

Ten systematic reviews (SRs) with eligibility criteria broader than this report were identified and network meta-analyses (NMAs) were included in three of them. Four evidence-based guidelines were identified. There were no direct comparisons between low-carbohydrate and standard diets in the primary studies in the SRs. Indirect comparisons between low-carbohydrate and standard diets were available in three NMAs with different scopes. One NMA found that low carbohydrate diets were significantly more effective in reducing triglyceride levels compared with the control diets, but insignificant for low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels. Another NMA included fewer primary studies in the NMA and concluded that low-carbohydrate diets were not significantly effective to reduce the levels of glycated hemoglobin (HbA1c), total cholesterol, and BMI, and increasing HDL cholesterol levels. The other NMA found low-carbohydrate diets significantly more effective in reducing HbA1c and fasting glucose levels.

The American Diabetes Association (ADA) guideline provides a recommendation that there is no single ideal dietary distribution of calories and individualized plans should be made. In the other recommendation, various diets are acceptable for the management of type 2 diabetes and low-carbohydrate diets are mentioned in the evidence review.

The Diabetes Canada guideline recommends that carbohydrate intake should be maintained to 45% to 60% of total energy.

The guideline by the Department of Veterans Affairs and the Department of Defense recommends 14% to 45% of energy from carbohydrate and/or foods with lower glycemic index in patients with type 2 diabetes who do not use the Mediterranean diet.

In the SIGN guideline, reducing dietary carbohydrate is recommended as one of the dietary options to lose weight and improve glycemic control in patients with type 2 diabetes.

The results were limited by the various definitions and classifications of dietary interventions and the lack of direct comparisons between low-carbohydrate and standard diets.

Due to the limitations, further research in the comparative effectiveness of low-carbohydrate diets in Canadian contexts may help reduce uncertainty in clinical decision making.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were type 2 diabetes and low carbohydrate diets. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials or controlled clinical trials or guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and October 1, 2019. Systematic

reviews and randomized controlled trials published between 2012 and 2017 previously identified in a 2017 CADTH report were also included.[6]

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with type 2 diabetes
Intervention	Diets that have a low carbohydrate component or referred to as low-carb (e.g., Low carbohydrate diet, Ketogenic diet, low-carbohydrate Mediterranean diet, low-carbohydrate vegetarian diet, Atkins diet)
Comparator	Q1: Standard diet (e.g., regular eating habits with no restriction by food group) Q2: Not applicable
Outcomes	Q1: Clinical effectiveness: glucose control (e.g., A1c levels, fasting plasma glucose), insulin sensitivity, reduction in drug/medication use, weight loss, weight gain, mortality, and morbidity, Safety (harms/risks/adverse events) Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2016. Guidelines with unclear methodology were also excluded. In the primary studies or systematic reviews, In order to be eligible for inclusion, diets needed to be specified as low-carbohydrate (For example, vegetarian diets were not assumed to be low-carbohydrate unless stated).

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 checklist.[9] Network meta-analyses (NMAs) were additionally assessed with the checklist developed by an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force.[10] Guidelines were assessed with the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 132 citations were identified in the literature search. Following screening of titles and abstracts, 101 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially

relevant articles, 20 publications were excluded for various reasons, and 14 publications met the inclusion criteria and were included in this report. These comprised ten systematic reviews (SRs), three of which included NMAs, and four evidence-based guidelines. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Study Design

There were ten systematic reviews with the eligibility criteria broader than those in this report.[4,13-21] Three SRs included NMAs.[14,15,18] Only randomized controlled trials or controlled trials were eligible for these SRs.[4,13-21] There were no primary studies in the SRs directly comparing low-carbohydrate diets with standard diets.[4,13-21] The effectiveness of low-carbohydrate diets was indirectly compared with standard or control diets in the three NMAs.[14,15,18] The overlap in the primary studies in the NMAs was demonstrated in Appendix 5.

The SRs were published in 2019 (five SRs),[4,13-16] 2018 (three SRs),[17-19] 2017 (one SR),[20] and 2013 (one SR).[21] Korsmo-Haugen et al. searched the literature published between 1983 and 2016.[13] McArdle et al. searched studies published between 1976 and 2018.[4] Neuenschwander et al. searched the publications released before January 2018.[14] Schwingshackl et al. searched articles published through July 2017.[18] Meng et al. searched references published through January 2017.[20] Ajala et al. searched studies published through August 2011.[21] In the SRs in which the search time frames were not reported, literature searches were conducted in 2016[17] and 2017.[15,19] Papamichou et al. did not report the search time frames or search dates.[16]

Four evidence-based guidelines were authored by different groups: the American Diabetes Association (ADA) guideline published in 2019,[5] Diabetes Canada guideline in 2018,[8] Department of Veterans Affairs and the Department of Defense (VA/DoD) guideline in 2017,[22] and Scottish Intercollegiate Guidelines Network (SIGN) guideline updated in 2017,[7] The guideline development and recommendation formation were based on methods that included comprehensive literature searches and systematic reviews for the research questions.[5,7,8,22] Multiple databases were searched and eligible studies were assessed for evidence strengths and limitations.[5,7,8,22]

Country of Origin

The first authors of the SRs were based in Norway (one SR),[13] UK (three SRs),[4,17,21] Germany (two SRs),[14,18] China (two SRs),[15,20] Australia (one SR),[16] and Indonesia (one SR).[19]

The guidelines were published in the US (two guidelines),[5] Canada (one guideline),[8] UK (one guideline).[7]

Patient Population

Studies including patients with type 2 diabetes were eligible for inclusion in all SRs.[4,13-21]

The intended users for the guidelines included all healthcare professionals involved in the care of people with diabetes and the target population were the patients with diabetes.[5,7,8,22]

Patients with type 2 diabetes were specifically targeted in the VA/DoD guideline,[22] while the other guidelines provided recommendations for both type 1 and type 2 diabetes.[8]

Interventions and Comparators

The interventions and comparators in the eligibility criteria in this report were low-carbohydrate and standard diets respectively. Korsmo-Haugen et al. compared diets below and above 40% of total energy from carbohydrates.[13] McArdle et al. compared active control diets with each other, including low-fat, low carbohydrate, and Mediterranean diets.[4] Neuenschwander et al. compared different dietary approaches in a NMA, including low-carbohydrate, low-fat, and moderate-carbohydrate diets.[14] Pan et al. compared Mediterranean, low-carbohydrate, low-fat, and regular diets with each other in a NMA.[15] Papamichou et al. compared low-carbohydrate, Mediterranean, vegetarian, vegan, intermittent-fasting, macrobiotic, and conventional low-fat diets with each other in a narrative synthesis.[16] Huntriss et al. compared low-carbohydrate diets with usual care that included any diets offered to patients.[17] Schwingshackl et al. compared low-fat, vegetarian, Mediterranean, high-protein, moderate-carbohydrate, low-carbohydrate, control, low glycemic index/load, Palaeolithic diets with each other in a NMA.[18] Suyoto et al. compared low-carbohydrate diets with those with higher proportions of carbohydrate.[19] Meng et al. compared low-carbohydrate diets with normal or high-carbohydrate diets.[20] Ajala et al. compared low-carbohydrate, vegetarian, vegan, low-glycemic index, high-fiber, Mediterranean, and high-protein diets with each other quantitatively.[21]

Pharmacological and non-pharmacological interventions for patients with diabetes to manage their conditions were considered in the identified guidelines.[5,7,8,22] Low-carbohydrate diets were considered in the guidelines.[5,7,8,22]

Outcomes

Korsmo-Haugen et al. assessed body weight, glycosylated haemoglobin (HbA1c, %), lipids, blood pressure, compliance with dietary interventions.[13] McArdle et al. evaluated carbohydrate intake and HbA1c.[4] Neuenschwander et al. investigated the levels of low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterols, and triglycerides.[14] Pan et al. assessed glycemic control, including HbA1c and fasting plasma glucose.[15] The secondary outcomes were cardiovascular risk factors, including total cholesterol and HDL cholesterol, and weight loss.[15] Papamichou et al. did not specify the outcomes they aimed to investigate and identified weight loss, lipid profile, HbA1c levels, need for diabetes medications, and glycemia in the primary studies.[16] The primary outcome for Huntriss et al. was HbA1c levels and the secondary outcomes included change in diabetes medications, weight, lipid profile, blood pressure, and dietary adherence.[17] Schwingshackl et al. assessed HbA1c levels or fasting glucose levels.[18] Suyoto et al. investigated the markers of renal function, including estimated glomerular filtration rates and creatinine clearance, or adverse events.[19] Meng et al. evaluated changes in weight loss, blood glucose, and blood lipid levels.[20] Ajala et al. assessed glycemic control, lipids, and weight loss.[21]

The outcomes considered in the guidelines included morbidity, mortality, and adverse events.[5,7,8,22]

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Summary of Critical Appraisal

Systematic reviews

The clarity of reporting is fundamental to the assessment of SRs. In all SRs, the population, intervention, comparator, and outcome components were described in the research questions and inclusion criteria.[4,13-21] The selection of study designs was described.[4,13-21] The populations, interventions, comparators, and outcomes of the included primary studies were described in the SRs.[4,13-21] The risk of bias assessment tools were reported in all SRs.[4,13-21] The review authors' conflicts of interest were declared in all SRs.[4,13-21] However, only Neuenschwander et al. and Schwingshackl et al. listed the excluded studies.[14,18] The minimal clinically important differences were not reported in the SRs.[4,13-21] The funding sources of the included studies were not reported in all SRs.[4,13-21] The role of the funding agencies in the primary studies were unclear.

The publication of review protocols helps to prevent duplicate reviews and understand the deviations from original protocols. However, the protocols of four SRs were not published *a priori*.[4,13-21]

Comprehensive literature searches and duplicate study selection and data extraction can minimize the risks of missing relevant evidence or human error related to inaccurate reporting of findings. Comprehensive literature searches were conducted in multiple databases in all SRs.[4,13-21] Except for Huntriss et al., Suyoto et al., and Ajala et al.,[17,19,21] the other author groups conducted study selection and data extraction in duplicate.[4,13-16,18,20]

Meta-analyses help to summarize the results from multiple primary studies. The precision and statistical power can improve by increasing sample sizes and aggregating the primary studies. Except for Papamichou et al. that narratively synthesized heterogenous primary studies,[16] all other author groups conducted meta-analyses with all or some of the primary studies depending on the heterogeneity between them.[4,13-15,17-21] Appropriate statistical methods were used.[4,13-15,17-21] The consideration of risk of bias in the primary studies can help authors to draw conclusions based on better-quality primary studies and, if possible, investigate the reasons contributing to the differences in results between primary studies. Risk of bias in the included studies were considered in the meta-analyses in seven SRs.[4,13-15,17-19] Publication bias was assessed in five SRs.[13,14,18-20]

There were NMAs conducted in three SRs.[14,15,18] The author groups identified several dietary interventions adopted in clinical practice.[14,15,18] However, they did not find sufficient information about the superiority of these approaches for the outcomes or patient groups they were interested in.[14,15,18] The methods section included the eligibility criteria, information sources, search strategies, study selection, and data extraction.[14,15,18] The outcome measures were reported.[14,15,18] The analysis methods were described and appropriate sensitivity analyses were planned and the results were presented.[14,15,18] The primary studies included in the network were described.[14,15,18] The results of direct and indirect comparisons were presented.[14,15,18] In the discussion, Neuenschwander et al. and Schwingshackl et al. provided result summaries and validity.[14,18] Because NMA is built on assumptions and statistical modeling it requires authors to assess assumptions and report the model fit to understand the plausibility of the results. However, model fit was not mentioned in the NMAs.[14,15,18]

Clinical guidelines

The objectives and the health questions in the four included guidelines were described.[5,7,8,22] The populations to whom the guideline aimed to target were reported.[5,7,8,22] The involvement of stakeholders helps to enrich the scope of clinical guidelines. Patients' perspectives had been sought in the four guidelines.[5,7,8,22] The target users were defined.[5,7,8,22] The clinical perspective can be understood based on the clinical experts consulted during guideline development. The experts involved in the guideline development were reported in three guidelines, including clinical experts and practitioners involved in diabetes care.[5,8,22] However, the experts involved in the development of the SIGN guideline development were not reported.[7]

The clarity in the reporting of the methods to develop guidance and formulate recommendations are critical to understand guideline validity. In the guidelines, systematic literature searches had been conducted in multiple databases,[7,8,22] except for the ADA guideline in which only MEDLINE was searched.[5,7] The criteria for study selection were described.[5,7,8,22] The strengths and limitations of the included studies were reported.[5,7,8,22] The health benefits and adverse effects were considered.[5,7,8,22] There were explicit links between the recommendations and the supporting evidence.[5,7,8,22] The guidelines were externally reviewed by experts.[5,7,8,22] A procedure to update the guideline was described in the VA/DoD and SIGN guidelines.[7,22] The methods for formulating the recommendations were described or referred to.[5,7,8,22]

Well-presented recommendations can help users to understand and use them. The recommendations in the four guidelines were specific and unambiguous.[5,7,8,22] There were options for managing health conditions if applicable.[5,7,8,22] The key recommendations were easily identifiable.[5,7,8,22]

Clear descriptions of guideline applicability are the key for the users to implement the recommendations. The facilitators and barriers, and advice regarding the implementation of recommendations were described if applicable.[5,7,8,22] The potential resource implications of applying the recommendations were considered if applicable.[5,7,8,22] Monitoring or auditing criteria may help users to understand the obstacles and feasibility of the recommendations. However, there were no monitoring or auditing criteria published in the four guidelines.[5,7,8,22]

The funding body did not claim to influence the content of the guidelines.[5,7,8,22] The competing interests of the guideline development group were reported in three guidelines,[5,8,22] and not for the SIGN guideline.[7]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Low-carbohydrate Diets

There were no direct comparisons between low-carbohydrate and standard diets identified in the primary studies in the SRs.[4,13-21] The evidence for the clinical effectiveness of low-carbohydrate diets relative to standard diets was based on indirect comparisons in the three NMAs.[14,15,18]

Low-density lipoprotein cholesterol

Neuenschwander et al. found that low-carbohydrate diets were not significantly more effective than the control diet (no or minimal intervention) in reducing the levels of LDL cholesterol.[14] However, Pan et al. did not identify enough primary studies to generate indirect comparisons for LDL cholesterol.[14,15]

High-density lipoprotein cholesterol

Neuenschwander et al. and Pan et al. found that low-carbohydrate diets were not significantly more effective than the control or regular diets in improving the levels of HDL cholesterol.[14,15]

Total cholesterol

Pan et al. identified that low-carbohydrate diets were not significantly more effective than regular diets in the NMA.[15]

Triglycerides

Neuenschwander et al. found that low-carbohydrate diets were significantly more effective than the control diets in reducing the levels of triglycerides.[14] However, Pan et al. concluded that low-carbohydrate diets were not significantly more effective than regular diets for this outcome.[15]

HbA1c

Pan et al. found that low-carbohydrate diets were not significantly more effective than regular diets in reducing the levels of HbA1c.[15] However, Schwingshackl et al. stated that low-carbohydrate diets were significantly more effective than the control diets.[18]

Fasting plasma glucose

There were not enough primary studies to generate indirect comparisons between low-carbohydrate and standard diets in the NMA by Pan et al.[15] Schwingshackl et al. found that low-carbohydrate diets were significantly more effective than the control diets in reducing fasting plasma glucose.[18]

Weight

Pan et al. did not identify enough primary studies to generate indirect comparison between low-carbohydrate and standard diets.[15]

Body mass index

Pan et al. found that low-carbohydrate diets were not significantly more effective that regular diets in reducing body mass index (BMI).[15]

Waist circumference

Pan et al. did not identify enough primary studies to generate indirect comparisons between low-carbohydrate and standard diets.[15]

Guidelines

The ADA guideline provides a level E recommendation (expert consensus or clinical experience) that suggests that there is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for patients with diabetes.[5] Instead, they recommend that

individualized plans should be made according to total calorie and metabolic goals.[5] In another recommendation (level B, supportive evidence from well-conducted cohort or case-control studies), various dietary interventions are acceptable for the management of type 2 diabetes.[5] In the evidence review, low-carbohydrate diets are mentioned for the potential to improve glycemic control.[5]

The Diabetes Canada guideline recommends that carbohydrate intake should be maintained to 45% to 60% of total energy with fats between 20% and 35% and proteins between 15% to 20% (level 4 or consensus).[8]

The VA/DoD guideline recommends 14% to 45% of energy from carbohydrates and/or foods with lower glycemic index in patients with type 2 diabetes who do not choose the Mediterranean diet (strong recommendation).[22]

The SIGN guideline provides a level B dietary recommendation that suggests reducing dietary carbohydrates is one of the options to lose weight and improve glycemic control in patients with type 2 diabetes, in addition to caloric restriction, reducing fat intake, and low-glycemic index diets.[7] The recommendation further noted that it seemed to be safe to consume a minimum of 50 grams of carbohydrates daily for up to six months when restricting total dietary carbohydrates.[7]

Appendix 4 presents a table of the main study findings and authors' conclusions.

Limitations

For dietary interventions, definitions were sometimes unclear and conflicting between studies. The same diet intervention could be classified differently in distinct SRs. For example, the diet intervention in a primary study included in several SRs was considered low-carbohydrate in the SRs by Neuenschwander et al., Pan et al., Papamichou et al., Huntriss et al., Schwingshackl et al., Suyoto et al., Meng et al., and Ajala et al.,[14-21] but very low carbohydrate in the SRs by Korsmo-Haugen et al. and McArdle et al.[4,13] The dietary interventions in several other primary studies were also categorized differently by the review authors.[4,13,18-21,23] Whether a diet intervention qualified as a Mediterranean diet was unclear in certain primary studies. For example, the low-carbohydrate diet in one primary study was considered Mediterranean in the SR by Huntriss et al.,[17] but not in other SRs that included the same primary study.[14-16,18] Low-carbohydrate diets were not defined uniformly.[14,15,18,19]

There are a variety of dietary interventions for diabetic patients.[21] Comparisons between various dietary interventions were published and low-carbohydrate diet interventions were often compared to low-fat diets in most SRs.[14-16,18,23] This was one of the reasons why there was a lack of direct comparisons between low-carbohydrate and standard diets.

In the SRs, the heterogeneity between the primary studies might not be well controlled. For example, the primary studies that were meta-analyzed did not have the same comparators.[23] There was a lack of direct comparisons between low-carbohydrate and standard diets. The evidence on the comparative effectiveness between low-carbohydrate and standard diets was based on indirect comparisons in NMAs.[14,15,18] Many of the indirect comparisons reported in these publications were based on the comparisons with low fat diets.[14,15,18] In the NMAs, interventions of different follow-up durations were pooled to estimate the comparative effectiveness of different dietary approaches.[14,15,18] The impact of between-study heterogeneity was unclear. Moreover, primary studies of different follow-up

durations, three to 48 months, were directly or indirectly compared in the NMAs.[14,15] The impact of merging studies of various follow-up durations was unclear.

Conclusions and Implications for Decision or Policy Making

Ten systematic reviews, three of which lacked independent literature selection and data extraction,[17,19,21] had eligibility criteria broader than those in this report and were included.[4,13-16,18,20] One updated clinical guideline was identified.[7] There were no primary studies directly comparing low-carbohydrate and standard diets identified in the SRs.[4,13-21] Indirect comparisons between low-carbohydrate and standard diets in three NMAs were identified.[14,15,18] Neuenschwander et al. found that low-carbohydrate diets were not significantly associated with the reduction in the levels of LDL and HDL cholesterol, but significantly more effective in reducing triglyceride levels compared with the control diets according to the indirect comparisons in the NMA.[14] Pan et al. summarized that low-carbohydrate diets were not significantly more effective than regular diets in reducing the levels of HbA1c, total cholesterol, and BMI and improving HDL cholesterol levels according to the indirect comparisons in a NMA.[15] There were insufficient primary studies to generate indirect comparisons for some outcomes, including fasting glucose levels, LDL cholesterol levels, weight, and waist circumference.[15] Schwingshackl et al. found low-carbohydrate diets significantly more effective in reducing HbA1c and fasting glucose levels than control diets (no or minimal intervention).[18]

The ADA guideline provides a recommendation that there is no single dietary distribution of calories for patients with diabetes and individualized plans should be made according to total calorie and metabolic goals (expert consensus or clinical experience).[5] Another recommendation is that various dietary interventions are acceptable for the management of type 2 diabetes (level B, supportive evidence from well-conducted cohort or case-control studies).[5]

The Diabetes Canada guideline recommends that carbohydrate intake should be maintained to 45% to 60% of total energy (level 4 or consensus).[8] Other dietary patterns, such as Mediterranean, vegan, and vegetarian diets, are also recommended.[8]

The VA/DoD guideline recommends that 14% to 45% of energy from carbohydrates and/or foods with lower glycemic index in patients with type 2 diabetes who do not take the Mediterranean diet (strong recommendation).[22]

The SIGN guideline recommends reducing dietary carbohydrate as one of the dietary options to lose weight and improve glycemic control in patients with type 2 diabetes, in addition to caloric restriction, reducing fat intake, and low-glycemic index diets (level B).[7]

This report had several limitations. The definitions of dietary interventions might vary between SRs.[14,15,18] The same dietary interventions might be classified differently in various SRs.[4,14] In the primary studies, low-carbohydrate diets were often compared to low-fat diets and were indirectly compared standard diets in three NMAs.[14,15,18] The scopes and conclusion of the NMAs were not exactly the same.[14,15,18]

Due to the lack of direct comparisons between low-carbohydrate and standard diets and the inconsistent conclusions between the NMAs, further research on the effectiveness of low-carbohydrate diets compared with standard diets in Canadian contexts may help reduce uncertainty in clinical decision-making.

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18. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *Eur J Epidemiol.* 2018;33(2):157-170.
19. Suyoto PST. Effect of low-carbohydrate diet on markers of renal function in patients with type 2 diabetes: a meta-analysis. *Diabetes Metab Res Rev.* 2018;34(7):e3032.
20. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract.* 2017;131:124-131.
21. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr.* 2013;97(3):505-516.
22. VA/DoD clinical practice guideline for the management of type 2 diabetes mellitus in primary care. Washingon (DC): Department of Veterans Affairs and Department of Defense; 2017: https://www.healthquality.va.gov/guidelines/CD/diabetes/VADoDDMCPGFinal508.pdf. Accessed 2019 Oct 30.
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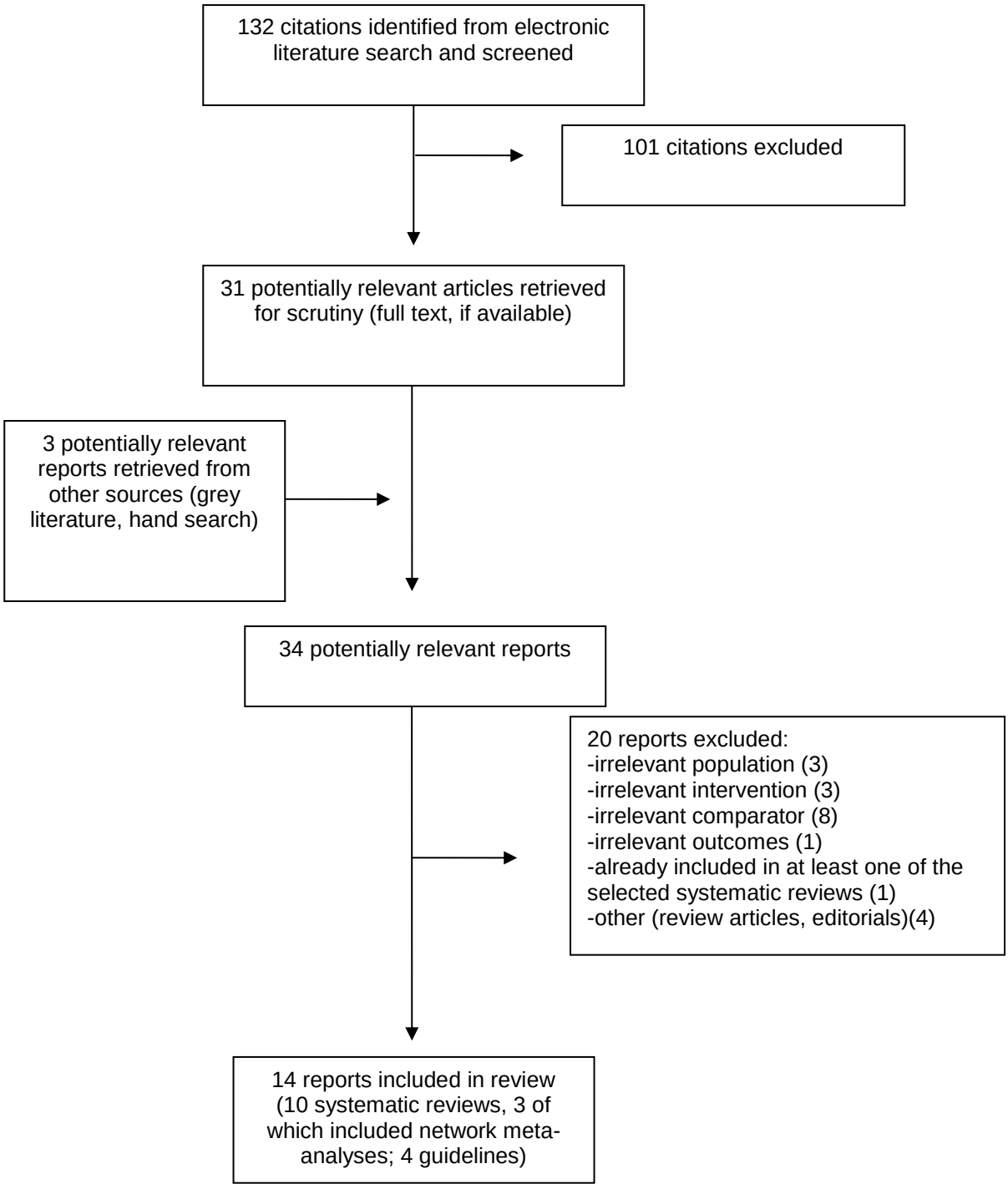
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Korsmo-Haugen et al. 2019,[13] Norway SR and MA	Inclusion criteria : randomized, controlled trials of parallel or cross-over design with a duration of more than 3 months 23 trials included No primary studies eligible for this report Multiple databases searched Language restrictions: English, Danish, Norwegian and Swedish Search time frame: 1983 to January 2016 PROSPERO registration : CRD42013005825	Inclusion criteria: adults with type 2 diabetes 2,178 diabetes patients included	Inclusion criteria: a diet below compared with a diet above 40% total energy from carbohydrate	Outcomes of interest: weight, glycosylated haemoglobin HbA1c (%), lipids, blood pressure and compliance with dietary intervention Follow-up durations: 3 months at least
McArdle et al. 2019,[4] UK SR and MA	Inclusion criteria: RCTs 25 RCTs included No primary studies eligible for this report Multiple databases searched Search time frame: 1976 to April 2018 No restriction on countries, languages and settings PROSPERO registration: CRD42015023586	Inclusion criteria: adults diagnosed with type 2 diabetes, a minimum intervention duration of 8 weeks and reported outcomes at a minimum of 12 weeks, and if the intervention restricted the proportion or quantity of dietary carbohydrate. 2,132 patients	Inclusion criteria: studies using active control diets (including low-fat, high-carbohydrate, low-glycaemic index, high-protein, Mediterranean and 'healthy eating'); carbohydrate restriction as intervention Definitions of low carbohydrate varied among the studies	Outcomes of interest: actual (self-reported or measured) carbohydrate intake during or at the end of the intervention and HbA1c Follow-up durations: 8 weeks at least

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Neuenschwander et al. 2019,[14] Germany SR and NMA	Inclusion criteria: RCTs 52 RCTs (44 for LDL, 48 for HDL and 52 for triglycerides) 16 RCTs in North America, 13 in Europe, 8 in Asia, and 15 in Australia and New Zealand Multiple databases searched Search time frame: until January 2018 PROSPERO registration: CRD42016047464	Inclusion criteria: patients with type 2 diabetes mellitus 5360 patients Age ranges: 44 to 65 years	Inclusion criteria: dietary approaches (energy restricted, isocaloric or ad libitum) Definitions: Low carbohydrate diet: < 25% carbohydrates of total energy intake; > 30% fat of total energy intake; high intake of animal and/or plant protein) Moderate carbohydrate diet: 25–45% carbohydrates total energy intake; 10–20% protein intake) Control diet: no intervention or minimal intervention	Outcomes of interest: LDL, HDL and/or triglycerides Follow-up durations: 3 to 48 months
Pan et al. 2019,[15] China SR and NMA	Inclusion criteria: randomized controlled trials and randomized cross-over trial 10 trials included Multiple databases searched Search dates: December 2016 and May 2017 Search time frame not reported PROSPERO registration: CRD42017056432	Inclusion criteria : patients with type 2 diabetes	Interventions of interest: Mediterranean, low-carbohydrate, low-fat diet, and regular diets Definitions: Low-carbohydrate diet: carbohydrate accounts for less than 26% (<130 of carbohydrate per day) total energy intake Regular diet: not defined	Primary outcome: "*glycemic control (including HbA1c, fasting plasma glucose)*" (p. 30) Secondary outcomes: "cardiovascular risk factors (including total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) and weight loss (including weight, body mass index [BMI], waist circumference)" (p. 30) Follow-up durations: not reported
Papamichou et al. 2019,[16] Australia SR without MA	Inclusion criteria : RCTs 20 RCTs	Inclusion criteria: adults with type 2 diabetes (>18 year of age)	Low carbohydrate, Mediterranean, vegetarian, vegan, intermittent fasting, macrobiotic, and	Outcomes of interest: not reported Outcomes identified: weight loss, lipid

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	No primary studies eligible for this report Multiple databases searched English articles only Search time frames and search dates: not available	Total sample sizes not reported 24 to 279 patients in the primary studies	conventional low-fat diets compared with each other	profile, HbA1c levels, need for diabetes medication, and glycemia Follow-up durations : 6 months at least
Huntriss et al. 2018,[17] UK SR and MA	Inclusion criteria : RCTs 18 RCTs included and 6 meta-analyzed No primary studies eligible for this report Multiple databases searched in June 2016 Search time frame: not reported English articles only PROSPERO registration: CRD42016035935	Inclusion criteria : adults aged 18 years or above with a diagnosis of type 2 diabetes 24 to 259 patients in the primary studies	Interventions of interest: low-carbohydrate diet as stated by the author Control: usual care, including a variety of diets that could be offered to patients as part of their diabetes care	Primary outcome: HbA1c (%) Secondary outcomes: change in diabetes medications, weight (kg), total, LDL and HDL cholesterol (mmol/L), triglycerides (mmol/L), systolic and diastolic blood pressure (mmHg), and dietary adherence Follow-up durations: 12 weeks to 4 years
Schwingshackl et al. 2018,[18] Germany SR and NMA	Inclusion criteria: RCTs 56 RCTs Multiple databases searched Search time frame: until July 2017 PROSPERO registration: CRD42016047464	Inclusion criteria: adults with type 2 diabetes mellitus 4937 patients identified Mean age range: 44 to 67 years	Dietary interventions identified: low-fat, Vegetarian, Mediterranean, high-protein, moderate-carbohydrate, low-carbohydrate, control, low glycaemic index/load, Palaeolithic Definitions: Low carbohydrate diet: < 25% carbohydrates of total energy intake; high intake of animal	Outcomes of interest: HbA1c (%) and/or fasting glucose (mmol/l) Follow-up durations: minimum intervention period of 12 weeks; 3 to 48 months

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			and/or plant protein; often high intake of fat Moderate-carbohydrate diet: 25–45% carbohydrates of total energy intake; 10–20% protein intake Control diet: no intervention or minimal intervention	
Suyoto et al. 2018,[19] Indonesia SR and MA	Inclusion criteria : controlled trial 12 trials No primary studies eligible to this report Multiple databases searched in September 2017	Inclusion criteria: patients with type 2 diabetes mellitus 942 patients	Interventions and comparators of interest: low-carbohydrate diet or control diet with higher proportion of carbohydrate Low-carbohydrate diet defined by the study authors Review authors' definition of low-carbohydrate diet: <200 g/d of carbohydrate or roughly 40% or less calories from carbohydrate	Outcomes of interest: marker of renal function (estimated glomerular filtration rate, creatinine clearance, urinary albumin, serum creatinine, and serum uric acid) or adverse event
Meng et al. 2017,[20] China SR and MA	Inclusion criteria : RCTs 9 RCTs included No primary studies eligible for this report Multiple databases searched Search time frame: through January 2017	Inclusion criteria: patients with type 2 diabetes mellitus 734 patients	Inclusion criteria: low carbohydrate diet (less than130 g carbohydrate/day or 26% of daily energy from carbohydrates) versus normal or high carbohydrate diet	Outcomes of interest: change in weight loss, blood glucose, and blood lipid levels
Ajala et al. 2013,[21] UK SR and MA	Inclusion criteria : RCTs conducted for at least 6 months, SRs, and MAs 20 RCTs included	Inclusion criteria: adults with type 2 diabetes 3,073 patients	Inclusion criteria: low-carbohydrate, vegetarian, vegan, low–glycemic index, high-fiber,	Outcomes of interest : glycemic control, lipids, and weight loss

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	No primary studies eligible for this report Multiple databases searched Search time frame : to August 2011		Mediterranean, and high-protein diets versus control diets including low-fat, high-glycemic index, American Diabetes Association, European Association for the Study of Diabetes, and low-protein diets	

HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MA = meta-analysis; NMA = network meta-analysis; PROSPERO = International Prospective Register of Systematic Reviews; RCT = randomized controlled trial; SR = systematic review

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
American Diabetes Association 2019,[5] US						
Healthcare professionals involved in the care of people with diabetes, patients with diabetes	Pharmacological and non-pharmacological interventions for diabetes	Morbidity, mortality, and adverse events	Systematic literature searches conducted in MEDLINE, and recommendations made based on the National Academy of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines methodology	Classification based on the National Academy of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines	Evidence synthesis and recommendation formulation based on the National Academy of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines and the feedback from the larger clinical community	Not reported
Diabetes Canada 2018,[8] Canada						
Healthcare professionals involved in the care of people with	Pharmacological and non-pharmacological interventions for diabetes	Morbidity, mortality, and adverse events	Systematic literature searches conducted in multiple databases,	Classification based on the Diabetes Canada methodology	Evidence synthesis and recommendation formulation based on the Diabetes Canada methodology, peer reviewed	Not reported

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
diabetes, patients with diabetes			independent study selection, and recommendations made based on the Diabetes Canada methodology			
Department of Veterans Affairs and the Department of Defense 2017,[22] US						
Healthcare professionals involved in the care of people with diabetes, patients with diabetes	Pharmacological and non-pharmacological interventions for diabetes	Morbidity, mortality, and adverse events	Systematic literature searches conducted in multiple databases, and recommendations made based on the methodology made by the Department of Veterans Affairs and the Department of Defense	Classification based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology	Evidence synthesis and recommendation formulation based on the Department of Veterans Affairs and the Department of Defense methodology, peer reviewed	Not reported
Scottish Intercollegiate Guidelines Network 2017 (update),[7] UK						
Healthcare professionals involved in the care of people with diabetes, patients with diabetes	Pharmacological and non-pharmacological interventions for diabetes	Morbidity, mortality, and adverse events	Systematic literature searches conducted in multiple databases, independent study selection, and recommendations made based on the Scottish Intercollegiate Guidelines Network (SIGN) methodology	Classification based on the SIGN 50 methodology	Evidence synthesis and recommendation formulation based on the SIGN 50 methodology	Not reported

GRADE = Grading of Recommendations Assessment, Development and Evaluation; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[9] and the ISPOR Network Meta-analysis checklist[10]

Strengths	Limitations
Korsmo-Haugen et al., 2019[13]	
- PICO components included in the research questions and inclusion criteria - Review protocol published *a priori* - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed - Publication bias assessed - Review authors' conflict of interest declared	- Excluded studies not provided - Sources of funding for the primary studies not reported
McArdle et al., 2019[4]	
- PICO components included in the research questions and inclusion criteria - Review protocol published *a priori* - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed - Review authors' conflict of interest declared	- Publication bias not assessed - Excluded studies not provided - Sources of funding for the primary studies not reported
Neuenschwander et al., 2019[14]	
- PICO components included in the research questions and inclusion criteria - Review protocol published *a priori* - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases	- Sources of funding for the primary studies not reported - Model fit in the network meta-analysis not reported

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[9] and the ISPOR Network Meta-analysis checklist[10]

Strengths	Limitations
- Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed - Review authors' conflict of interest declared - A list of excluded studies provided - Publication bias assessed - Study rationale and study objectives stated - Eligibility criteria, search strategy, study selection process, and data extraction stated in the Methods - Outcome measures described - Analysis model and framework described - Sensitivity analysis planned and the results presented - Summary of the network meta-analysis presented - Results of the network meta-analysis presented - The validity of the network meta-analysis discussed	
Pan et al., 2019[15]	
- PICO components included in the research questions and inclusion criteria - Review protocol published *a priori* - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed - Review authors' conflict of interest declared - Study rationale and study objectives stated - Eligibility criteria, search strategy, study selection process, and data extraction stated in the Methods - Outcome measures described - Analysis model and framework described - Sensitivity analysis planned and the results presented - Summary of the network meta-analysis presented - Results of the network meta-analysis presented	- The validity of the network meta-analysis not discussed - A list of excluded studies not provided - Publication bias not assessed - Sources of funding for the primary studies not reported - Model fit in the network meta-analysis not reported

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[9] and the ISPOR Network Meta-analysis checklist[10]

Strengths	Limitations
Papamichou et al., 2019[16]	
- PICO components included in the research questions and inclusion criteria - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Review authors' conflict of interest declared	- Excluded studies not provided - Sources of funding for the primary studies not reported - Review protocol not published *a priori* - Risk of bias in the primary studies not considered while interpreting the results - Heterogeneity between the primary studies not discussed - Publication bias not assessed
Huntriss et al., 2018[17]	
- PICO components included in the research questions and inclusion criteria - Review protocol published *a priori* - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed - Review authors' conflict of interest declared	- Excluded studies not provided - Sources of funding for the primary studies not reported - Study selection not in duplicate - Data extraction not in duplicate - Publication bias not assessed
Schwingshackl et al., 2018[18]	
- PICO components included in the research questions and inclusion criteria - Review protocol published *a priori* - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - A list of excluded studies provided - Study selection in duplicate - Data extraction in duplicate - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed	- Publication bias not assessed - Sources of funding for the primary studies not reported - Model fit in the network meta-analysis not reported

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[9] and the ISPOR Network Meta-analysis checklist[10]

Strengths	Limitations
- Review authors' conflict of interest declared - Study rationale and study objectives stated - Eligibility criteria, search strategy, study selection process, and data extraction stated in the Methods - Outcome measures described - Analysis model and framework described - Sensitivity analysis planned and the results presented - Summary of the network meta-analysis presented - Results of the network meta-analysis presented - The validity of the network meta-analysis discussed	
Suyoto et al., 2018[19]	
- PICO components included in the research questions and inclusion criteria - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Included studies described - Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - The impact of the risk of bias in the primary studies assessed in the meta-analysis - Publication bias assessed - Review authors' conflict of interest declared	- Review protocol not published *a priori* - Excluded studies not provided - Sources of funding for the primary studies not reported - Study selection not in duplicate - Data extraction not in duplicate - Risk of bias in the primary studies not considered while interpreting the results - Heterogeneity between the primary studies not discussed
Meng et al., 2017[20]	
- PICO components included in the research questions and inclusion criteria - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Included studies described - Study selection in duplicate - Data extraction in duplicate - Risk of bias in the included studies assessed - Appropriate statistical methods used for meta-analysis - Risk of bias in the primary studies considered while interpreting the results - Heterogeneity between the primary studies discussed - Review authors' conflict of interest declared - Publication bias assessed	- Review protocol not published *a priori* - Excluded studies not provided - Sources of funding for the primary studies not reported - The impact of the risk of bias in the primary studies not assessed in the meta-analysis
Ajala et al., 2013[21]	
- PICO components included in the research questions and inclusion criteria - Study designs for inclusion explained, not justified - Comprehensive literature searches conducted in multiple databases - Included studies described	- Excluded studies not provided - Sources of funding for the primary studies not reported - Study selection not in duplicate - Data extraction not in duplicate - Publication bias not assessed - Review protocol not published *a priori*

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[9] and the ISPOR Network Meta-analysis checklist[10]

Strengths	Limitations
- Risk of bias in the included studies assessed with the Cochrane checklist - Appropriate statistical methods used for meta-analysis - Heterogeneity between the primary studies discussed - Review authors' conflict of interest declared	- The impact of the risk of bias in the primary studies not assessed in the meta-analysis - Risk of bias in the primary studies considered while interpreting the results

AMSTAR = A Measurement Tool to Assess Systematic Reviews; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; PICO = population, intervention, comparator, and outcomes

Table 5: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline			
	American Diabetes Association, 2019[5]	Diabetes Canada, 2018[8]	Department of Veterans Affairs and the Department of Defense, 2017[22]	Scottish Intercollegiate Guidelines Network, 2017 (update)[7]
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Not reported
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Yes	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	Yes	Yes

Table 5: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline			
	American Diabetes Association, 2019[5]	Diabetes Canada, 2018[8]	Department of Veterans Affairs and the Department of Defense, 2017[22]	Scottish Intercollegiate Guidelines Network, 2017 (update)[7]
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes	Yes	Yes
14. A procedure for updating the guideline is provided.	Not reported	Not reported	Yes	Yes
Domain 4: Clarity of Presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes, if applicable	Yes, if applicable	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Yes, if applicable	Yes	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	Yes	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No	No	No
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	No

AGREE = Appraisal of Guidelines for Research and Evaluation.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion[a]
Korsmo-Haugen et al., 2019[13]	
A diet below compared with a diet above 40% total energy from carbohydrate - No primary studies comparing low-carbohydrate diets with standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.
McArdle et al., 2019[4]	
Carbohydrate restriction compared with other diets - No primary studies comparing low-carbohydrate diets with standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.
Neuenschwander et al., 2019[14]	
Dietary approaches compared with each other (NMA) - No direct comparisons between low-carbohydrate diets and standard diets (or control diets) - Indirect comparisons between low-carbohydrate diets and standard diets LDL-cholesterol - Low-carbohydrate diet not significantly more effective than the control diet: mean difference = -0.05 mmol/L (95% CI, -0.25 to 0.16), indirect comparison) HDL-cholesterol - Low-carbohydrate diets not significantly more effective than the control diets: mean difference = 0.06 mmol/L (95% CI, -0.01 to 0.12), indirect comparison Triglycerides - Low-carbohydrate diets significantly more effective than the control diets: mean difference, -0.36 mmol/L (95% CI = -0.62 to -0.10), indirect comparison	Low credibility of evidence is a major limitation.
Pan et al., 2019[15]	
Dietary interventions compared with each other (NMA) - Low-carbohydrate diets compared to regular diets in indirect comparisons HbA1c - Low-carbohydrate diets not significantly more effective than regular diets: mean difference = 0.13% (95% CI, -0.99 to 1.25) Fasting plasma glucose - No evidence Total cholesterol	A conclusion about Mediterranean diets was made. No specific conclusion low-carbohydrate diets was made.

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion[a]
- Low-carbohydrate diets not significantly more effective than regular diets: mean difference = -0.24 mmol/L (95% CI, -0.99, 0.50) HDL-cholesterol - Low-carbohydrate diets not significantly more effective than regular diets: mean difference = -0.04 mmol/L (95% CI, -0.22 to 0.15) LDL-cholesterol - No evidence Triglycerides - Low-carbohydrate diets not significantly more effective than regular diets: mean difference = -0.10 mmol/L (95% CI, -0.80 to 0.60) Weight (kg) - No evidence BMI (unit free) - Low-carbohydrate diets not significantly more effective than regular diets: mean difference = -0.97 (95% CI, -4.00 to 2.05) Waist circumference (cm) - No evidence	
Papamichou et al., 2019[16]	
Dietary approaches compared with each other - No primary studies comparing low-carbohydrate diets with standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.
Huntriss et al., 2018[17]	
Low-carbohydrate diets compared with usual care - No primary studies comparing low-carbohydrate diets with standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.
Schwingshackl et al., 2018[18]	
Dietary interventions compared with each other (NMA) HbA1c (%) - Low-carbohydrate diets significantly more effective than the control diets: mean difference = -0.82 (95% CI, -1.11 to -0.53), indirect comparison Fasting glucose (mmol/l) - Low-carbohydrate diets significantly more effective than the control diets: mean difference = -1.23 (95% CI, -1.91 to -0.55)	- "*The network analysis also revealed that all dietary approaches significantly reduce HbA1c (- 0.82 to - 0.47% reduction) and fasting glucose (- 1.61 to - 1.00 mmol/l reduction) compared to a control diet*" (p. 157)
Suyoto et al., 2018[19]	

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion[a]
Low-carbohydrate diets versus diets with higher proportions of carbohydrate Renal function - No primary studies comparing low-carbohydrate diets with standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.
Meng et al., 2017[20]	
Low-carbohydrate diets versus normal- or high-carbohydrate diets - No primary studies comparing low-carbohydrate diets with standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.
Ajala et al., 2013[21]	
Dietary interventions compared with each other - No primary studies comparing low-carbohydrate diets and standard diets	Not applicable as no primary studies comparing low-carbohydrate diets with standard diets were found.

[a]Conclusions relevant to the comparison between low-carbohydrate and standard diets reported. Studies may include conclusions based on other comparisons not reported here.

CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; GDM = gestational diabetes mellitus; GI = glycemic index; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LCD = low-carbohydrate diet; LDL = low-density lipoprotein; NMA = network meta-analysis

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
American Diabetes Association, 2019[5]	
- "*5.10 There is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for people with diabetes; therefore, meal plans should be individualized while keeping total calorie and metabolic goals in mind*" (p. S49) - "*5.11Avariety of eating patterns are acceptable for the management of type 2 diabetes and prediabetes*" (p. S49) (low-carbohydrate diets: one of the diets mentioned to improve glycemic control)	Evidence rating - E (Expert consensus or clinical experience) - B (Supportive evidence from well-conducted cohort studies; Supportive evidence from a well-conducted case-control study)
Diabetes Canada, 2018[8]	
- "*6. In adults with diabetes, the macronutrient distribution as a percentage of total energy can range from 45% to 60% carbohydrate, 15% to 20% protein and 20% to 35% fat to allow for individualization of nutrition therapy based on preferences and treatment goals*" (p. S74) - "*12. The following dietary patterns may be considered in people with type 2 diabetes, incorporating patient preferences, including:*	Strengths of evidence; strengths of recommendations - Grade D [The best evidence was at Level 4 (studies that did not meet higher quality criteria for evidence, such as systematic reviews, randomized controlled trials, non-randomized controlled studies) or consensus]; Consensus

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
a. Mediterranean-style dietary pattern to reduce major CV events [Grade A, Level 1A (143)] and improve glycemic control [Grade B, Level 2 (50,139)].	- Grade A (The best evidence was at Level 1), Level 1A (Systematic overview or meta-analysis of high-quality RCTs OR Appropriately designed RCT with adequate power to answer the question posed by the investigators); Grade B (The best evidence was at Level 2), Level 2 (RCT or systematic overview that does not meet Level 1 criteria)
b. Vegan or vegetarian dietary pattern to improve glycemic control [Grade B, Level 2 (145,251)], body weight [Grade C, Level 3 (148)], and blood lipids, including LDL-C [Grade B, Level 2 (149)] and reduce myocardial infarction risk [Grade B, Level 2 (152)].	- Grade B, Level 2; Grade C (The best evidence was at Level 3), Level 3 (Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies); Grade B, Level 2; Grade B, Level 2
c. DASH dietary pattern to improve glycemic control [Grade C, Level 2 (159)], BP [Grade D, Level 4 (156–159)], and LDL-C [Grade B, Level 2 (158,159)] and reduce major CV events [Grade B, Level 3 (161)].	- Grade C, Level 2; Grade D, Level 3; Grade B, Level 2; Grade B, Level 3
d. Dietary patterns emphasizing dietary pulses (e.g. beans, peas, chickpeas, lentils) to improve glycemic control [Grade B, Level 2 (176)], systolic BP [Grade C, Level 2 (178)] and body weight [Grade B, Level 2 (179)].	- Grade B, Level 2; Grade C, Level 2; Grade B, Level 2
e. Dietary patterns emphasizing fruit and vegetables to improve glycemic control [Grade B, Level 2 (183,184)] and reduce CV mortality [Grade C, Level 3 (79)].	- Grade B, Level 2; Grade C, Level 3
f. Dietary patterns emphasizing nuts to improve glycemic control [Grade B, Level 2 (188)], and LDL-C [Grade B, Level 2 (190)]" (p. S74)	- Grade B, Level 2; Grade, Level 2
Department of Veterans Affairs and the Department of Defense, 2017[22]	
- "*14. We recommend a nutrition intervention strategy reducing percent of energy from carbohydrate to 14-45% per day and/or foods with lower glycemic index in patients with type 2 diabetes who do not choose the Mediterranean diet*" (p. 22)	Strengths of recommendation: strong
Scottish Intercollegiate Guidelines Network, 2014 (update)[7]	
- "*People with type 2 diabetes can be given dietary choices for achieving weight loss that may also improve glycaemic control. Options include simple caloric restriction, reducing fat intake, consumption of carbohydrates with low rather than high glycaemic index, and restricting the total amount of dietary carbohydrate (a minimum of 50 g per day appears safe for up to six months).*" (p. 22)	Strength of evidence - 1+: "*Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias*" (page number not assigned) - 1-: "*Meta-analyses, systematic reviews, or RCTs with a high risk of bias*" (page number not assigned) Strength of recommendation - B: "*A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+*" (page number not assigned)

DASH = Dietary Approaches to Stop Hypertension; LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial; SR = systematic review

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Neuenschwander et al., 2019[14] (52 RCTs)	Pan et al., 2019[15] (10 RCTs)	Schwingshackl et al., 2018[18] (56 trials)
Brehm 2009	x		x
Brunerova 2007	x		x
Coppell 2010			x
Daly 2005			x
Davis 2009		x	x
Davis 2011		x	
de Bont 1981	x		x
Dyson 2007	x		x
Guldbrand 2012	x	x	x
Heilbronn 1999	x		x
Hockaday 1978	x		x
Iqbal 2009	x		x
Jonasson 2014		x	
Ma 2008			x
McLaughlin 2007	x		
Milne 1994	x		x
Rock 2014	x		x
Saslow 2014	x		x
Sato 2016	x		x
Shai 2008			x
Shige 2000	x		x
Stern 2004			x
Tay 2015	x		x
Walker 1995	x		x
Westman 2008	x		x
Yamada 2014	x		x

Only the primary studies assessing low-carbohydrate diets were listed.

Appendix 6: Additional References of Potential Interest

Guidelines with Unclear Methodology

Aschner PM, Munoz OM, Giron D, et al. Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults. *Colomb Med.* 2016;47(2):109-131.

Chang CR, Francois ME, Little JP. Restricting carbohydrates at breakfast is sufficient to reduce 24-hour exposure to postprandial hyperglycemia and improve glycemic variability. *Am J Clin Nutr.* 2019;109(5):1302-1309

Reviews without comprehensive literature searches

Magnusdottir OK, Gunnarsdottir I, Birgisdottir BE. Dietary guidelines in type 2 diabetes: the Nordic diet or the ketogenic diet? *Curr Opin Endocrinol Diabetes Obes.* 2017;24(5):315-319.

Non-randomized studies

Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Ther.* 2018;9(2):583-612.

Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol (Lausanne).* 2019;10:348.