Reduced carbohydrate diets

No. 2021/41Ke, The Hague, November 16, 2021

Background document to:
Dutch dietary guidelines for people with type 2 diabetes
No. 2021/41e, The Hague, November 16, 2021

Health Council of the Netherlands

contents

01 introduction

This background document belongs to the advisory report *Dutch Dietary Guidelines for people with type 2 diabetes*.[1] It describes the methodology for the search, selection and evaluation of the literature regarding the effects of reduced carbohydrate diets on health outcomes in people with type 2 diabetes. The current background document furthermore describes the evidence on this topic and the conclusions that have been drawn by the Health Council's Committee on Nutrition.

02 methodology

2.1 Questions

The Committee aimed to answer the following questions:

1. What is the effect of advising a low or moderate carbohydrate diet compared with a diet high in carbohydrates on health outcomes in people with type 2 diabetes?
2. Are there differential effects when carbohydrates are advised to be substituted by either protein or fat in the reduced carbohydrate diets, in people with type 2 diabetes?

The Committee aimed to distinguish between short and longer-term effects.

2.2 Current carbohydrate recommendations

The Health Council of the Netherlands recommends that the adult population derives at least 40% up to 70% of total energy intake (en%) from the diet out of carbohydrates.[2] The average carbohydrate intake of the Dutch adult population is 43 en% according to the most recent *Dutch National Food Consumption Survey*.[3] There are no Health Council recommendations regarding carbohydrate intake for people with type 2 diabetes.

2.3 Low, moderate and high carbohydrate diets

In scientific literature, the terms *low carbohydrate diet* and *reduced carbohydrate diet* are generally used to indicate study diets that are lower in carbohydrate amount (grams or en%) than the comparator diet. There is no standard definition of a low or reduced carbohydrate diet. As a consequence, there are differences between low or reduced carbohydrate diets described in scientific literature. Nevertheless, the classification of carbohydrates proposed by Feinman et al.[4] is widely adopted, including in meta-analyses (MAs) relevant to this topic.[5] This classification was therefore used by the Committee to categorise the carbohydrate quantities of the diets. The following cut-offs were used:

- very low: 20 to 50 grams per day (g/d); ≤10 en% (this diet is also known as the ketogenic diet);
- low: >50 to <130 g/d; >10 to <26 en%;
- moderate: 130 to 230 g/d; 26 to 45 en%;
- high: >230 g/d; >45 en%.

A further explanation for the rationale behind those cut-offs, given by Feinman et al.[4], is presented in **Annex A**.

In classifying studies according to the level of carbohydrate restriction, the Committee based this on the en% of carbohydrates prescribed to the low or moderate carbohydrate diet group. Where no energy percentages were presented, g/d were used.

In its evaluation, the Committee separated the effects of 1) low and very low, and 2) moderate carbohydrate diets, where possible. The categories very low and low were combined into one subgroup since relatively few

studies addressed very low carbohydrate diets. For ease of reading, this category is often referred to as low carbohydrate diets in the text below. The Committee aimed to use the average consumption of adults in the Netherlands (43 en%)[3] as the reference with which diets reduced in carbohydrates were compared. However, since the average consumption of the Dutch adult population falls in the top end of the range of moderate carbohydrate diets, comparisons were made with diets that were higher in carbohydrates: >45 en%.

2.3.1 Substitution effects

Given that the effects of reduced carbohydrate diets could differ depending on whether the carbohydrates would be substituted by (subgroups of) fat or protein[6], the Committee additionally separated evidence of studies that substituted 1) carbohydrates with fat, and 2) carbohydrates with protein, where possible. The Committee preferred to further evaluate substitutions of carbohydrates by subgroups of fat (e.g. saturated fat [SFA], monounsaturated fat [MUFA], polyunsaturated fat [PUFA]) and protein (e.g. derived from animal versus vegetable sources). However, such distinctions could not be made since there were too few studies per subgroup of fat substitution, and there was generally no information on the subtypes for protein. Due to this limitation, conclusions on differential substitution effects between fat and protein were formulated with caution and were formulated as “speculations on potential differential effects” instead of firm conclusions.

2.3.2 Isocaloric diets

Study diets were defined as isocaloric when the authors stated so in the original randomised controlled trial (RCT) publication and/or when the prescribed energy intake in the intervention and control groups were similar. When prescribed energy intakes were lacking, achieved energy intakes were used to judge whether the study diets were isocaloric. When no information was given on those three components, it was assumed that the study diets were not isocaloric.

2.4 Outcomes

The Committee selected the following health outcomes for this advisory report. A detailed motivation is provided in the background document *Methodology for the evaluation of evidence*:[7]

Surrogate outcomes:

- Glycated haemoglobin (HbA1c);
- Fasting blood glucose;
- Body weight;
- Systolic blood pressure;
- Low-density lipoprotein (LDL) cholesterol;
- Estimated glomerular filtration rate (eGFR).

Long-term health outcomes:

- Morbidity and/or mortality from total cardiovascular diseases (CVD), total cancer, coronary heart disease (CHD), stroke, heart failure, chronic obstructive pulmonary disease (COPD), breast cancer, colorectal cancer, lung cancer, dementia, depression, chronic kidney disease;
- All-cause mortality.

Other:

- Diabetes remission: HbA1c <48 mmol/mol and no use of diabetes medication for ≥1 year;
- Diabetes reversion: HbA1c <53 mmol/mol and less medication use for ≥1 year.

Only literature on the surrogate outcomes turned out to be available within the inclusion criteria of the Committee. Therefore, literature regarding long-term health outcomes or diabetes remission and reversion was not evaluated in the current background document.

2.5 Selection and evaluation of literature

A detailed description of the approach used by the Committee for selecting and evaluating scientific literature is given in the background document *Methodology for the evaluation of evidence*.[7] To summarise, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs) with MAs of prospective cohort studies and RCTs examining the effects or associations of reduced carbohydrate diets with health outcomes in people with type 2 diabetes.

No SRs with MAs of prospective cohort studies were found. Therefore, the Committee only evaluated evidence from RCT studies. Where possible, the Committee evaluated SR with MA of RCTs that separately analysed effects of (very) low carbohydrate diets and moderate carbohydrate diets. In addition, the Committee complemented the evidence from SRs with MAs with recent evidence from individual RCTs that were not included in the SRs with MAs.

The Committee used the report of the Scientific Advisory Committee on Nutrition (SACN; United Kingdom) as the starting point for the selection of scientific literature and extraction of data.[8] A SACN working group summarised the scientific evidence regarding the effects of reduced carbohydrate diets on HbA1c, fasting glucose, body weight and LDL cholesterol. The literature selection from the *draft* version of the SACN report, published online in 2020, was used by the Committee. In that *draft* report, SRs with MAs published until September 2018 were evaluated. Where needed, additional information was abstracted from the articles underlying the SACN report.

The Committee supplemented the literature and data selected by SACN with the following scientific literature:

1. SRs with MAs published after the literature inclusion date of the SACN working group;
2. SRs with MAs of selected outcomes not included by the SACN working group;
3. Individual RCTs published after the inclusion date of the most recent SR with MA.

Individual RCTs that addressed energy restrictions along with carbohydrate restrictions compared with no or less strict energy restriction in the control group were excluded from the Committee's evaluation. In addition, RCTs with a duration shorter than 3 months were excluded.
An overview of the search strategies, selection of articles, and flow diagram of the literature searches is presented in **Annex B**.

2.5.1 Selection per outcome

In Table 1, an overview is given of the MAs and recent RCTs selected by the Committee for its evaluation of the selected health outcomes. A more extensive description of the selection of literature is presented in Annex B.

For HbA1c and body weight, the effects of (very) low carbohydrate diets and moderate carbohydrate diets, and short and long-term effects, were separately analysed in the selected MA.

For the remaining outcomes, no MAs were available that separated effects of both (very) low carbohydrate diets and moderate carbohydrate diets, and short and long-term effects. For those outcomes, MAs separated by study duration were selected. In case no heterogeneity between studies was present, the Committee argued the reported effects are likely similar for low and moderate carbohydrate diets (given that both interventions were sufficiently addressed in the MA). In case there was unexplained heterogeneity, the Committee visually inspected the forest plots to argue whether heterogeneity could be explained by the extent of carbohydrate restriction and whether separate conclusions regarding effects of low and moderate carbohydrate diets could be drawn.

It should be noted that all MAs used for the remaining outcomes, except Huntriss et al.[9], applied a 40 en% cut off for defining reduced carbohydrate diets, which deviates from the cut off chosen by the Committee (45 en%). The MA of Huntriss et al. did not use a particular cut-off for defining reduced carbohydrate diets. Instead, that MA specified reduced carbohydrate diets as diets that were lower in carbohydrates than the comparator diet. The MA of van Zuuren et al.[10] only included studies with a low fat (≤ 30 en%) comparator diet. Also, van Zuuren et al. only included studies in the MA where the achieved intakes of carbohydrates and fat did not exceed 2% above the limits defined for carbohydrates (40 en%) and fat (30 en%).

Table 1 Meta-analyses and recent RCTs selected by the Committee for the evaluation of the effects of advising reduced carbohydrate diets on health outcomes.

Health outcome	Short or longer term[a]	Meta-analyses	Recent RCTs
HbA1c	Short term	Sainsbury et al.[5], 2018 McArdle et al.[11], 2019	Liu et al.[12], 2018 Wang et al.[13], 2018
HbA1c, body weight	Longer term	Sainsbury et al.[5], 2018	Saslow et al.[14], 2017 Tay et al.[15], 2018 Sato et al.[16], 2017
Body weight	Short term	Sainsbury et al.[5], 2018 McArdle et al.[11], 2019	Struik et al.[17], 2020
Fasting plasma glucose	Short term	Van Zuuren et al.[10], 2018	Liu et al.[12], 2018 Wang et al.[13], 2018
Fasting plasma glucose	Longer term	Van Zuuren et al.[10], 2018	Tay et al.[15], 2018
LDL cholesterol	Short term	Korsmo-Haugen et al.[18], 2019 van Zuuren et al.[10], 2018	Liu et al.[12], 2018
LDL cholesterol	Longer term	Korsmo-Haugen et al.[18], 2019 Huntriss et al.[9], 2018	Saslow et al.[14], 2017 Tay et al.[15], 2018 Sato et al.[16], 2017
Systolic blood pressure	Short term	Korsmo-Haugen et al.[18], 2019 van Zuuren et al.[10], 2018	Liu et al.[12], 2018
Systolic blood pressure	Longer term	Korsmo-Haugen et al.[18], 2019 Huntriss et al.[9], 2018	
eGFR	Short and longer term combined	Suyoto et al.[19], 2018	Liu et al.[12], 2018

eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; LDL: low-density lipoprotein; RCT: randomised controlled trial.

[a] The Committee defined short term as 3 to 6 months, and longer term in principle as 12 months or longer.

The Committee noted two potentially relevant SRs with MAs published after their search date for SRs with MAs (June 2020). First of all, Silverii et al.[20], published a report of a SR with MA that addressed combined low and moderate carbohydrate diets, and low carbohydrate diets separately, and their effects on HbA1c and body weight, in July 2020. However, all studies included in the MA of low carbohydrate diets were also included in the already selected MA, and therefore this article was not taken into account. Second, in January 2021, the Committee noted the publication of Goldenberg et al.[21], which addressed the effects of low carbohydrate diets on health outcomes in people with type 2 diabetes. That article included several additional RCTs and health outcomes (diabetes remission). At the time of publication of the MA, the current background document was already in a phase of finalisation. Therefore, it was not feasible to fully ingrate this MA into the background document. As an alternative to taking the MA into account in their evaluation, the Committee discussed the impact of the findings of the recent MA on their conclusions in a separate section at the end of this background document (Section 3.8), and concluded that the new MA findings would not change their conclusions.

2.5.2 Evaluation of substitution effects

For the evaluation of substitution effects by protein and fat, data from relevant individual RCTs were abstracted from the selected SRs and MAs and recent RCTs (Table 1). The Committee marked RCTs as substitution with fat in case prescribed protein intake was similar between the reduced and high carbohydrate diet groups, and the prescribed intakes of fat were higher in the reduced carbohydrate groups compared with the high carbohydrate diet group. The Committee marked RCTs as substitution with protein in case prescribed fat intake was similar between the reduced and

high carbohydrate diet groups and the prescribed intakes of protein were higher in the reduced carbohydrate groups compared with high carbohydrate diet groups. Where *prescribed* protein and fat intakes were lacking, the classification was based on *achieved* intakes. Intakes of protein and fat were marked as comparable when intakes of the reduced carbohydrate group did not differ more than 5% from the intakes in the control group. The remaining studies were classified as substitutions with a combination of protein and fat.

2.5.3 Short and long-term effects on surrogate outcomes

The Committee defined short-term studies into surrogate outcomes as 3 to 6 months, and long term in principle as 12 months or longer. Two RCTs with 9 and 11-months durations were included in the longer-term evaluations as well.

2.5.4 Subgroup effects

The Committee aimed to additionally evaluate whether effects of reduced carbohydrate diets differed in subgroups of sex, body weight status, medication use and duration of diabetes. This was evaluated on the MA level. However, it turned out such subgroup analyses were not performed in any of the included MAs, and therefore it was impossible to draw conclusions on subgroup effects. In this context, it should be noted that the majority of participants included in the studies were overweight or obese. This limits the possibility to compare effects in overweight and obese participants with normal-weight participants and suggests that the current evaluation is particularly applicable to people with type 2 diabetes with overweight or obesity.

2.5.5 Risk of bias

The MAs included in the evaluations used the Cochrane risk of bias tool, 2011 version, to assess the risk of bias in the included RCTs.[22]
The following domains were evaluated: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; other bias (such as potential conflicts of interest). For the recently published individual RCTs, the Committee assessed risk of bias with the 2019 version of the Cochrane risk of bias tool.[23] The following five domains were evaluated: bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the reported result.

It is important to note that blinding of participants and personnel is not feasible in the type of studies under investigation. Therefore, the Committee did not take this aspect into account when judging the risk of bias in the recent, individual RCTs. One of the MAs, of Korsmo-Haugen et al.[18], did not take this domain into account either when judging the risk of bias, whereas the other MAs did. Furthermore, the Committee noted that

drop outs are of particular concern in the types of study under evaluation, particularly in the longer term. Therefore, the Committee specifically described retention rates and risk of bias due to incomplete outcome data in its evaluations.

2.6 Drawing conclusions

A detailed description of the approach used for drawing conclusions is given in the background document *Methodology for the evaluation of evidence*.[7] To summarise, conclusions on the certainty of the evidence regarding the effects of low and moderate carbohydrate diets on health outcomes were drawn based on the number of studies and participants that contributed to the evaluation. Moreover, the Committee took the risk of bias and heterogeneity between studies into account in order to judge the certainty of the evidence. The Committee used the decision tree (**Annex L**) as a tool to support consistency in drawing conclusions.

Separate speculations were made on differential effects for fat and protein substitutions when three or more RCTs were available within each subgroup that specifically addressed fat or protein substitutions.

2.6.1 Interpretation of conclusions

The evaluated studies were mostly of dietary advice and not of providing foods to the participants. Therefore, the Committee drew conclusions regarding the effect of *advising* reduced carbohydrate diets instead of actually *consuming* reduced carbohydrate diets. The benefit of this approach is that it is in accordance with everyday practice. The Committee sees the level of dietary compliance as part of the effect under study. Therefore, low compliance does not reduce the quality of the evidence but can be considered an explanation for no or attenuated effects.

Moreover, the evaluated studies generally evaluated the effects of reduced versus high carbohydrate diets in the context of recommendations to reduce body weight and/or to reduce energy intake. It was therefore not possible for the Committee to conclude on whether the reported effects of reduced versus high carbohydrate diets also apply to situations that are not targeted at weight loss and/or caloric restriction. The advice to the intervention (reduced carbohydrate diet) and the advice to the control (high carbohydrate diet) groups were given in the context of recommendations to reduce body weight and/or to reduce energy intake. Moderate carbohydrate diet interventions were often (advised to be) restricted in energy intake and were predominantly isocaloric compared with the control diet. The (very) low carbohydrate interventions were predominantly not isocaloric compared with the control diet. In the case of (very) low carbohydrate diet interventions, energy restriction was often not part of the advice, but this was expected to happen automatically due to the restricted choice in foods due to the restrictions on carbohydrates.

03
effects of low and moderate carbohydrate diets on health outcomes

Below, the scientific evidence for the effects of advising low and moderate carbohydrate diets on health outcomes in people with type 2 diabetes is described. This chapter starts with a summary of the conclusions, followed by evaluations per health outcome.

The risk of bias assessments and funding sources for all RCTs included in the evaluations are presented in **Annex K**.

3.1 Summary of conclusions

In Table 2, a summary of the conclusions is given regarding the effects of advising low and moderate carbohydrate diets compared with high carbohydrate diets on the selected health outcomes.

Table 2 Overview of conclusions regarding the effects of advising low and moderate carbohydrate diets compared with high carbohydrate diets on health outcomes in people with type 2 diabetes.

Health outcome	Low carbohydrate diets, short term effects	Low carbohydrate diets, longer term effects	Moderate carbohydrate diets, short term effects	Moderate carbohydrate diets, longer term effects
HbA1c	Reduction of 0.36 to 0.49%; Strong evidence	No difference	No difference	No difference
Body weight	*3 months:* Reduction of 2.5 kg; Strong evidence *6 months:* No difference; Strong evidence	No difference	No difference	Reduction of 0.6 kg; Limited evidence
Fasting glucose	Reducing effect; limited evidence	Too little research	Too little research	Too little research
LDL cholesterol	No difference	Contradictory evidence	No difference	Contradictory evidence
Systolic blood pressure	Too little research	Too little research	Too little research	Too little research
eGFR	Too little research	Too little research	Too little research	Too little research

eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; LDL: low-density lipoprotein.

Furthermore, the Committee concluded the following with respect to substitution effects and dietary compliance:

Substitution effects: Carbohydrates in the low and moderate carbohydrate diets were recommended to be substituted by either protein or fat or a combination of the two. The types of protein were not specified. Fat substitutions were specified in a selection of RCTs and were predominantly MUFA substitutions, sometimes combined with either PUFA or SFA. In most of the evaluations, there was too little research available to speculate on potential differences in effects when the carbohydrates were advised to be substituted by either fat or protein. Comparisons of effects of advising fat or protein substitutions were possible for a few moderate carbohydrate diet evaluations. In all of those evaluations, it was concluded that the effects of advising moderate carbohydrate diets compared with high carbohydrate diets did not noticeably differ when it was advised to substitute the carbohydrates in the moderate carbohydrate diet with either fat or protein. There were too few studies to allow further subgroup analyses by type of fat substitution and no studies to allow subgroup analyses by type of protein substitution.

Dietary compliance: Overall, compliance with the very low carbohydrate diet (≤ 10 en% carbohydrates) was poor, and achieved intakes were within the range of low carbohydrate diets (>10 to < 26 en% carbohydrates) instead of very low carbohydrate diets, both in the short and long term. For low carbohydrate diets, compliance was variable in the short term and poor in the long term. Compliance with moderate carbohydrate diets was generally good, although, in the longer term, the contrast in achieved carbohydrate intakes with the control group was small in some of the RCTs. These issues with compliance may have contributed to the lack of effect, or effects of little clinical meaning, found in the majority of evaluations.

3.2 HbA1c

3.2.1 Short-term effects on HbA1c

Table 3 summarises the results and characteristics of the MAs that provided evidence regarding the effects of advising low and moderate carbohydrate diets on HbA1c in the short term. In addition, Table 4 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MAs and the individual RCTs are provided in **Annex C**.

Table 3 Short-term effects of advising low and moderate carbohydrate diets on HbA1c in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; study duration	Sainsbury, 2018[5]; 3 months	Sainsbury, 2018[5]; 6 months	McArdle, 2019[11]; 3 to 6 months	Sainsbury, 2018[5]; 3 months	Sainsbury, 2018[5]; 6 months
Category of carbohydrate restriction	Low carbohydrate diets	Low carbohydrate diets	Low carbohydrate diets	Moderate carbohydrate diets	Moderate carbohydrate diets
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: <26 en%; c: >45 en%	i: <26 en%; c: >45 en%	i: 10 to 26 en%; c: 'higher' (NR)	i: 26 to 45 en%; c: >45 en%	i: 26 to 45 en%; c: >5 en%
Number of studies; total number of participants	4 RCTs; 421, including 4 with pre-diabetes[b]	5 RCTs; 328	5 RCTs; 239	8 RCTs; 632	6 RCTs; 875, including 30 people with type 1 diabetes[d]
Heterogeneity	No: 0%	No: 0%	No: 0%	No: 0%	Yes: 59%
Strength of the effect: WMD[a] (95%CI)	-0.47% [-5.2 mmol/mol] (95%CI -0.71, -0.23)	-0.36% [-4.0 mmol/mol] (95%CI -0.62, -0.09)	-0.49% [-5.4 mmol/mol] (95%CI -0.75, -0.23)	-0.06% [-6.6 mmol/mol] (95%CI -0.17, 0.06)	-0.06% [-6.6 mmol/mol] (95%CI -0.25, 0.13)
Study population	People diagnosed with type 2 diabetes and pre-diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin; Europe, USA	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]:oral agents, insulin; Europe, USA, Japan	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin; Europe, Japan	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin, and none (diet only) in one RCT[e]; Europe, Canada, USA, Australia	People diagnosed with type 2 and type 1 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin; USA, Canada, Australia, New Zeeland

CI: confidence interval; NR: not reported; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean differen ce in HbA1c change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;
[b] The RCT of Saslow et al.[24] (2014) included 34 participants of whom 4 had pre-diabetes and 30 type 2 diabetes;
[c] Diabetes medications represent the types of medications that were used among the participants of the included RCTs (it does not mean that *all* participants in all included RCTs used those medications);
[d] One RCT, of Stychar et al.[25], contributed people with type 1 diabetes. This RCT included 30 participants;
[e] One RCT, of Wolever et al.[26], included participants that did not use any diabetes medications (oral agents or insulin).

Table 4 Short-term effects of advising moderate carbohydrate diets on HbA1c in people with type 2 diabetes: individual RCTs.

RCT; Study duration	Liu, 2018[12]; 3 months	Wang, 2018[13]; 3 months
Category of carbohydrate restriction	Moderate carbohydrate diet	Moderate carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 42 en%; c: 54 en%	i: <45 en%; c: NR
Number of participants in intervention (i) and control (c) group	i: 30; c: 30	i: 28; c: 28
Strength of the effect: Mean difference (95%CI)	-0.24% [-2.6 mmol/mol] (95%CI -0.43, -0.05)	-1.04% [-11.44 mmol/mol] (95%CI NR; p-value from t-test: 0.004)
Study population	People newly diagnosed with type 2 diabetes; men and women; BMI[a]: 24 kg/m2 (i) and 25 kg/m^2 (c); diabetes medications: none (diet only); China (Asia)	People diagnosed with type 2 diabetes; diabetes duration[a]: 13 (i) and 9 (c) years; men and women; BMI[a]: 22 kg/m^2 (i) and 21 kg/m^2 (c); diabetes medications[b]: oral agents, insulin; China (Asia)

BMI: body mass index; CI: confidence interval; NR: not reported; RCT: randomised controlled trial.

[a] BMI and diabetes duration values represent the average in the study population;

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

The Committee concluded the following:

Low carbohydrate diets

Intervention studies show that advising low carbohydrate diets compared with advising diets high in carbohydrates reduces HbA1c with 4.0 to 5.4 mmol/mol [0.36 to 0.49%] within 3 to 6 months, in people diagnosed with type 2 diabetes. The evidence is strong.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 10 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong.
2. There is no obvious heterogeneity in directions of effects between RCTs.
3. There is a statistically significant reducing effect in the evaluated MAs.
4. The Committee noted some studies had moderate retention rates, and one of the included RCTs was at high risk of bias (among others, due to the risk of incomplete outcome data). However, the Committee expects this likely did not noticeably impact the conclusions, since 1) there was the lack of heterogeneity between studies, and 2) excluding the study at high risk of bias did not change the conclusions, and 3) another study with moderate retention (which was not scored as being at high risk of bias) had a minor weight in the MA. Based on this, the

Committee drew its conclusion, and there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that very low carbohydrate diet studies had low dietary compliance, and for low carbohydrate diet studies, the compliance was variable. This may have attenuated the effect sizes of the evaluated RCTs. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the lower compliance can be seen as part of the effect under evaluation and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

Intervention studies show there is likely no difference in the effects of advising moderate carbohydrate diets compared with advising diets high in carbohydrates on HbA1c within 3 to 6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 13 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is no obvious heterogeneity in directions of effects between RCTs when discarding one RCT performed among people with type 1 diabetes (that RCT was rather small and unlikely affected the MA conclusion).
3. There is no statistically significant effect in the MAs.
4. The Committee noted that, despite the MAs not finding effects on HbA1c, two recent individual RCTs reported relatively large reducing effects on HbA1c that were statistically significant. However, those RCTs were small in numbers of included participants and unlikely to change the conclusions of the MAs.
5. Moreover, the Committee noted some studies had moderate retention rates, and four of the included RCTs were at high risk of bias (among others due to risk of incomplete outcome data). However, excluding

studies at high risk of bias did not change the conclusions of the MAs. The two other studies with moderate retention (that were not scored as being at high risk of bias) had minor weights in the MAs, and were therefore unlikely to affect the conclusions. Based on this, the Committee concluded that there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that compliance with the moderate carbohydrate diets was good overall and therefore unlikely to have contributed to the lack of effect.

Regarding substitution effects: The effects of advising moderate carbohydrate diets compared with high carbohydrate diets did not noticeably differ when it was advised to substitute the carbohydrates in the moderate carbohydrate diet with either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

Two MAs, of Sainsbury et al.[5] and McArdle et al.[11] were included in the evaluation of low carbohydrate diets.

The MA of Sainsbury et al. combined studies with very low and low carbohydrate intakes in the low carbohydrate diet group. The MA of Sainsbury et al. presented separate results for RCTs with a duration of 3 months (one RCT actually had a duration of 4 months) and 6 months (one RCT actually had a duration of 8 months). There were 4 RCTs (2 very low and 2 low carbohydrate diets) included in the 3 months' evaluation and 5 RCTs (2 very low and 3 low carbohydrate diets) in the 6 months' evaluation. In the 3 months' MA of Sainsbury et al., the RCTs of Saslow et al.[24] and Daly et al.[27] had the largest weights. The RCT of Davis et al.[28] had the largest weight in the 6 months' MA.

The MA of McArdle et al. evaluated 5 low carbohydrate diet RCTs with durations of 3 to 6 months. In this MA, the RCTs of Daly et al., Jonasson et al.[29] and Sato et al.[30] had the largest weights. Two out of the 5 RCTs overlapped with those included by Sainsbury et al.

In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. In a majority of studies, the control group

was advised to reduce calorie intake, and the intervention group was advised to reduce carbohydrate intake (with an automatic reduction in energy intake as a consequence). Two of the included RCTs (one included by Sainsbury et al. and one included by McArdle et al.) were isocaloric. The remaining RCTs were not. Comparator diets were often defined as low fat, and/or reduced calorie diets. Two were defined as conventional calorie-restricted or diabetes diets.

Both MAs found small, yet statistically significant, greater reductions in HbA1c with advising low compared with high carbohydrate diets. The magnitudes of effects ranged from a weighted mean difference (WMD) in HbA1c change of -4.0 to -5.4 mmol/mol (0.36 to 0.49%). This means that HbA1c levels of people with type 2 diabetes advised to consume lower carbohydrate diets were reduced by 4.0 to 5.4 mmol/mol (0.36 to 0.49%) more during the intervention period than the HbA1c levels of people with type 2 diabetes advised to consume high carbohydrate diets.

No heterogeneity between RCTs was found for the 3 and 6-month analyses of Sainsbury et al. and the analyses of McArdle et al.

Subgroup and sensitivity analyses

Sainsbury et al.[5] tested the effect of weight loss on the primary MA of HbA1c change by omitting studies with significantly greater weight loss on the lower carbohydrate diet. These analyses were possible for the 6-month data only and showed no difference in effects between the low and high carbohydrate diets on HbA1c (WMD -0.24% (95%CI: -0.55, 0.07)), suggesting the effects of advising low carbohydrate diets on HbA1c are driven by weight loss.

No other relevant subgroup analyses were performed in both MAs.

Substitution of carbohydrates

In all RCTs, carbohydrates in the low carbohydrate diet were advised to be substituted by a combination of fat and protein. Subgroup analyses by protein or fat substitution were therefore not possible. In most RCTs, the types of fat that substituted the carbohydrates were not specified. Where specified, it was a combination of MUFA and PUFA or a combination of MUFA and SFA.

Retention rates

Retention rates ranged from 55 to 100% in the (very) low carbohydrate diet groups, and 46 to 100% in the control groups in the RCTs included by Sainsbury et al.[5] RCTs included by McArdle et al.[11] had retention rates that ranged from 78 to 100% in the low carbohydrate diet groups, and from 76 to 100% in the control groups.

Risk of bias

In the MA of Sainsbury et al.[5], one RCT, of Westman et al.[31] (very low carbohydrate diet intervention), was scored as high risk of bias because of incomplete outcome data, with low retention rates, differences in retention rates between groups, and last observation carried forward (LOCF) analyses for missing values. In addition, only a small sample of food diaries was analysed (15 in total, out of 84 participants). Moreover, an unclear other risk of bias was detected due to funding provided by the Atkins Foundation. The funders' involvement in the study was not specified. Excluding this study resulted in no material change of results, with a WMD in HbA1c change of -0.45% (95%CI: -0.69, -0.20) at 3 months and -0.31% (95%CI: -0.59, -0.04) at 6 months.

In addition to the RCT of Westman et al., the RCT of Samaha et al.[32] (included in 6-month analyses of Sainsbury et al.), is worth noting due to a high drop-out rate in both study groups (35 and 54%). LOCF was used for missing HbA1c measurements of those who dropped out, and there were no reasons given for dropout. There are no analyses available that exclude this study. However, given the lack of heterogeneity between studies and moderate weight of this study in the MA, it is not expected that results have been affected by including this study.

The MA of McArdle et al.[11] did not report the overall risk of bias per individual RCT. Nevertheless, McArdle et al. reported that all RCTs were scored as low to moderate risk of bias.

Sainsbury et al. reported that the overall quality of the evidence was scored as low due to high risk of performance and detection bias, and inconsistency in the estimates of the effect across studies.

Sainsbury et al. reported that there was publication bias present in the 3-month analysis but not in the 6-month analysis. This concerns analyses of combined low and moderate carbohydrate diet RCTs. It is therefore unclear whether those findings are specifically applicable to studies into the effects of advising low carbohydrate diets.

McArdle et al. did not give information on the overall quality of the evidence and publication bias.

Dietary compliance

For the 3 very low carbohydrate diet interventions included in the MA of Sainsbury et al.[5], achieved carbohydrate intakes in the very low carbohydrate diet groups were higher than prescribed, and were within the range of low carbohydrate diets. Moreover, in the MA of Sainsbury et al., achieved carbohydrate intake in the low carbohydrate diet groups was higher than prescribed, and within the range of a moderate carbohydrate

diet, in the RCT of Davis et al.[28] That RCT had a relatively large weight in the MA. Achieved intakes in the remaining 3 low carbohydrate RCTs were generally higher than prescribed as well, but were still within the range of a low carbohydrate diet.

In the MA of McArdle et al.[11], for most RCTs, achieved intakes were generally higher than prescribed, but within the range of a low carbohydrate diet, except the RCT of Jonsson et al.[33] In that RCT, achieved intakes were comparable to a moderate carbohydrate diet.

Low dietary compliance in some of the RCTs may have attenuated the effect sizes of those studies.

Summary

The MAs of Sainsbury et al.[11] and McArdle et al.[11] showed that HbA1c levels were reduced by 4.0 to 5.4 mmol/mol more when people with type 2 diabetes were advised to consume (very) low carbohydrate diets compared with control diets over a period of 3 to 6 months. There was no heterogeneity between studies. The studies advised overall to substitute the carbohydrates in the low carbohydrate diet with a combination of fat and protein. Some of the RCTs selected by Sainsbury et al. and McArdle et al. had low retention rates, and one study included in the MA of Sainsbury et al. was at high overall risk of bias. Due to the lack of heterogeneity between studies, it is not expected that such RCTs have noticeably impacted the results of the MAs. Dietary compliance with very low carbohydrate diets was rather low, and variable for low carbohydrate diets. This may have attenuated effect sizes of some of the included RCTs.

Moderate carbohydrate diets

Study characteristics and main effects

One MA, of Sainsbury et al.[5], was included in the evaluation of the effect of advising a moderate carbohydrate diet, with 8 RCTs contributing to the 3-month data and 6 to the 6-month data. The RCT of Wolever et al.[26] had a relatively large weight in both the 3 and 6-month MA. One of the RCTs included in the 6-month MA, of Stychar et al.[25], was performed among people with type 1 diabetes. Unfortunately, no analysis excluding the RCT of Stychar et al. was available. The study included only 30 participants and contributed 10% weight to the MA.

In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. All but one (Wolever et al.) of the included RCTs were isocaloric. Comparator diets were often defined as high carbohydrate, low fat, and/or low protein diets. Two were defined as standard diabetic diets.

When advising moderate carbohydrate diets, no differences in effects on HbA1c change compared with advising high carbohydrate dies were found

in the MA of Sainsbury et al. at both 3 and 6 months (WMD for HbA1c change: -0.06% (95%CI -0.17, 0.06) and -0.06% (95%CI -0.25 0.13), respectively). There was no heterogeneity between studies for the 3-month analyses. For the 6-month analyses, there was substantial heterogeneity (59%). This heterogeneity at 6 months was likely (partly) due to the RCT of Stycher et al., that was performed among people with type 1 diabetes. The Committee expected that the MA conclusion of no effect would not have changed if the RCT of Stychar had been excluded.

Two recent individual RCTs, of Wang et al.[13] and Liu et al.[12] were included in the evaluation of moderate carbohydrate diets as well. Both had a duration of 3 months. The RCT of Wang et al. included 56 participants, was not isocaloric, and defined the comparator diet as a low fat diet. The RCT of Liu et al. included 60 participants, was isocaloric, and defined the comparator diet as a high carbohydrate, low protein diet.

In contrast to the MA findings, the two recent RCTs did find statistically significantly greater reductions in HbA1c among participants who were advised moderate carbohydrate diets compared with control groups. Compared with the other RCTs used in the MA, Wang et al. reported rather large differences in achieved carbohydrate intakes between the moderate and high carbohydrate diet groups (39 vs 56 en%), which may be one of the explanations for the differences in results. However, given the relatively small sample sizes of the RCTs compared with the overall sample size of the MA, it is not expected that those recent RCTs impact the overall MA conclusion.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in the MA of Sainsbury et al.[5]

Substitution of carbohydrates

In 5 RCTs, carbohydrates in the moderate carbohydrate diets were advised to be substituted by fat. Where the type of fat was specified (3 out of the 5 RCTs), it were predominantly MUFAs. In another 5 RCTs, carbohydrates were advised to be substituted by protein. The type of protein was not reported. For two RCTs, carbohydrates were advised to be substituted by a combination of protein and fat, with the fat being a combination of MUFA with either PUFA or SFA. Effects per RCT are shown in Table 5. In general, the effects were larger for studies that substituted with fat than with protein. However, most RCTs showed no statistically significant effect.

Table 5 Short-term effects of advising moderate carbohydrate diets compared with high carbohydrate diets on HbA1c change (%): RCTs with substitutions for protein, fat or a combination of protein and fat.

RCT	Substitution(s)	Mean difference (95%CI) in HbA1c change (%)
Krebs, 2012[34]	Protein	-0.01 (-0.22, 0.20)
Larsen, 2011[35]	Protein	-0.03 (-0.21, 0.15)
Liu, 2018[12]	Protein	-0.24 (-0.43, -0.05)
Luger, 2013[36]	Protein	-0.10 (-0.84, 0.64)
Parker, 2002[37]	Protein	-0.03 (-0.42, 0.36)
Brehm, 2009[38]	Fat	3m: -0.20 (-0.58, 0.18); 6m: -0.30 (-0.76, 0.16)
Brunerova, 2007[39]	Fat	-0.40 (-1.09, 0.29)
Fabricatore, 2011[40]	Fat	-0.40 (-0.66, -0.14)
Wang, 2018[13]	Fat	-1.04 (95%CI NR; p-value: 0.004)
Wolever, 2008[26]	Fat	3m: 0.03 (-0.17, 0.23); 6m: 0.02 (-0.14, 0.18)
Watson, 2016[41]	Fat & protein	3m: -0.23 (-0.78, 0.32); 6m: 0.16 (-0.44, 0.76)
Wycherley, 2010[42]	Fat & protein	-0.70 (-1.65, 0.25)

CI: confidence interval; m: months; NR: not reported; RCT: randomised controlled trial.

Retention rates

For the studies that reported retention rates at 3 or 6 months, the majority of RCTs reported retention rates of 82% or higher, except two RCTs (Wycherley et al.[42] and Watson et al.[41]), that reported retention rates of 57% (moderate carbohydrate diet group) and 72% (both intervention and control group). Both RCTs had relatively little weight in the MA and this is unlikely to have affected the MA result.

Risk of bias

In the MA of Sainsbury et al.[5], three RCTs included in the 3-month analysis (Brunerova et al.[39], Parker et al.[37] and Wolever et al.[26]) were scored as high overall risk of bias.

The RCT of Brunerova et al. was scored as high risk of bias due to selective reporting. The participants' dietary intake was not reported, but methods state that this information was collected. Moreover, there were unclarities regarding the completeness of data since there was no flow-chart of participant recruitment and retention, and no reporting of attrition.

The RCT of Parker et al. was scored as high risk of bias due to incomplete outcome data. This was due to completers-only analysis at 3 and 12 months, and poor retention rates at 12 months (38 out of 66 participants). Those concerns are particularly relevant for the long-term evaluation, and less for the current evaluation of short term (3-month) effects.
The retention rate at 3 months was 54 out of 66 participants.

The RCT of Wolever et al. was scored as high risk of bias due to incomplete outcome data. Data were reported for completers only. At 12 months follow-up, approximately 20% had dropped out in each group. Unfortunately, drop-out rates were not reported for the 3 months analyses. Also, a high risk of another type of bias was detected since the first author is president and part-owner of GI Index Testing Inc. The RCT had

relatively large weights in the MA of 3 months. Nevertheless, excluding the studies at high risk of bias, including the study of Wolever et al., did not noticeably affect the MA results, with WMD in HbA1c change of -0.09% (95%CI: -0.24, 0.06; I^2 not reported).

The individual RCTs of Liu et al.[12] and Wang et al.[13] were both judged as being not at high risk of bias.

In the 6-month MA of Sainsbury et al., the RCTs of Wolever et al. and Stychar et al.[25] were scored as high risk of bias. The reasons behind the high risk of bias in the RCT of Wolever et al. have been described above. The RCT of Stychar et al. was scored as high risk of bias due to selective reporting. The reporting of participants' dietary intake was limited, whereas methods state this information was collected. The MA findings did not substantially change after excluding both RCTs (WMD -0.17 (95%CI -0.42, 0.09), I^2 not reported).

Sainsbury et al. reported that the overall quality of the evidence was scored as low due to high risk of performance and detection bias, and inconsistency in the estimates of the effect across studies.

Sainsbury et al. reported that there was publication bias present in the 3-month analysis but not in the 6-month analysis. This concerns analyses of combined low and moderate carbohydrate diet RCTs. It is therefore unclear whether those findings are specifically applicable to studies into the effects of advising moderate carbohydrate diets.

Compliance

For the RCTs that reported achieved dietary intakes at 3 or 6 months, the achieved carbohydrate intakes were in line with the prescribed intakes. This suggests participants complied with the study diets.

Summary

The MA of Sainsbury et al.[5] did not find differences in short-term effects on HbA1c of advising moderate compared with high carbohydrate diets, with no to moderate heterogeneity between studies. The effects of advising moderate carbohydrate diets on HbA1c reductions appeared larger for studies that advised substitution of carbohydrates with fat. Nevertheless, most of those RCTs found no statistically significant effects. Retention rates were acceptable for most RCTs and the lower retention rates in a few RCTs are unlikely to have affected the MA results. Four RCTs were scored as high risk of bias. However, excluding those RCTs did not affect MA conclusions. There was good compliance with the moderate carbohydrate diets.

3.2.2 Longer-term effects on HbA1c

Table 6 summarises the results and characteristics of the MAs that provided evidence regarding the effects of advising low and moderate

carbohydrate diets on HbA1c in the longer term. In addition, Table 7 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MAs and the individual RCTs are provided in **Annex D**.

Table 6 Long-term effects of advising low and moderate carbohydrate diets on HbA1c in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Sainsbury, 2018[5]; 12 months	Sainsbury, 2018[5]; 9 to 12 months
Category of carbohydrate restriction	Low carbohydrate diets	Moderate carbohydrate diets
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: <26 en%; c: >45 en%	i: 26 to 45 en%; c: >45 en%
Number of studies; total number of participants	4 RCTs; 335	8 RCTs; 1293
Heterogeneity	No: 0%	Moderate: 30%
Strength of the effect: WMD[a] (95%CI)	-0.17% [-1.87 mmol/mol] (95%CI -0.44, 0.09)	-0.08% [-0.88 mmol/mol] (95%CI -0.23, 0.06)
Study population	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[b]: oral agents, insulin; Europe, USA, Australia	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[b]: oral agents, insulin, and none (diet only) in one RCT[c]; USA, Australia, Asia, New Zeeland

CI: confidence interval; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean difference in HbA1c change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] Diabetes medications represent the types of medications that were used among the participants of the included RCTs (it does not mean that *all* participants in all included RCTs used those medications);

[c] One RCT of Wolever et al.26 included participants that did not use any diabetes medications (oral agents or insulin).

Table 7 Long-term effects of advising moderate carbohydrate diets on HbA1c in people with type 2 diabetes: individual RCTs.

RCT; Study duration	Saslow, 2017[14]; 12 months	Sato, 2017[16]; 18 months	Tay, 2018[15]; 24 months
Category of carbohydrate restriction	Very low carbohydrate diet	Low carbohydrate diet	Low carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 20 to 50 g; c: 45 to 50 en%	i: 130 g; c: 50 to 60 en%	i: 14 en%; c: 53 en%
Number of participants in intervention (i) and control (c) group	i: 16; c: 18	i: 33; c: 33	i: 58; c: 57
Strength of the effect: Mean difference[a] (95%CI)	-0.3%; 95%CI: NR; p-value 0.007[b]	0.05%; 95%CI: NR; p-value 1.00[c]	0.3%; 95%CI: NR; p-value 0.52[b]
Study population	People diagnosed with type 2 diabetes or pre-diabetes; diabetes duration[d]: 7 years; men and women; BMI[d]: 37 kg/m^2; diabetes medications[e]: oral agents; USA	People diagnosed with type 2 diabetes; diabetes duration: 13 (i) and 14 (c) years; men and women; BMI[d]: 27 kg/m^2; diabetes medications[e]: oral agents, insulin; Japan	People diagnosed with type 2 diabetes; diabetes duration: 7 years; men and women; BMI[d]: 35 kg/m^2; diabetes medications[e]: oral agents insulin; Australia

CI: confidence interval; NR: not reported; RCT: randomised controlled trial; USA: United States of America.

[a] Values are the differences in estimated marginal mean changes between low and high carbohydrate diet groups;

[b] Derived from mixed effects linear regression model;

[c] p-values were derived from Mann-Whitney U test;

[d] BMI and diabetes duration values represent the average in the study population;

[e] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

The Committee concluded the following:

Low carbohydrate diets

Intervention studies show there is likely no difference in the effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on HbA1c within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 7 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is no obvious heterogeneity in direction of the effects between studies.
3. There is no statistically significant effect in the MA, and this is overall supported by recent RCTs.
4. The Committee noted that some studies had moderate retention rates. However, the Committee expects this is unlikely to have impacted the conclusions since there was no heterogeneity between studies. Also, the study with the lowest retention rate had a minor weight in the MA. Finally, none of the included studies was scored as high risk of bias. Based on this, the Committee made its conclusion and there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that long-term compliance with the (very) low carbohydrate diets was poor overall. This may (partly) explain the lack of effect found in the MA. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the poor compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when carbohydrates are advised to be substituted with either fat or protein.

Moderate carbohydrate diets

Intervention studies show there is likely no difference in the effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on HbA1c within 9 to 12 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 8 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is only minor heterogeneity in directions of effects between RCTs.
3. There is no statistically significant effect in the MA.
4. The Committee noted that a selection of studies had moderate retention rates, and two studies were at high risk of bias, among others, due to incomplete outcome data. However, the Committee expects this is unlikely to have impacted the conclusions since excluding studies at high risk of bias did not change the MA conclusion, and the remaining studies with moderate retention had only minor weights in the MA. Based on this, the Committee concluded that there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that contrasts in achieved intakes of carbohydrates between the intervention and control groups were small. This may (partly) explain the lack of effect found in the MA. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: The effects of advising moderate carbohydrate diets compared with high carbohydrate diets did not noticeably differ when it was advised to substitute the carbohydrates in the moderate carbohydrate diet with either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

The MA of Sainsbury et al.[5] was included in the evaluation of low carbohydrate diets. The MA included 4 RCTs with a total number of 335

participants. Of those 4 RCTs, one was classified as very low carbohydrate intervention and the remaining as low carbohydrate interventions. All RCTs had a duration of 12 months. The RCTs of Davis et al.[28] and Tay et al.[43] (2015) had the largest weights in the MA.

In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Two of the included RCTs were isocaloric, whereas the other two were not. Comparator diets were often defined as low fat, and/or reduced calorie diets.

No effect of advising low carbohydrate diets compared with high carbohydrate diets on HbA1c was found, with a WMD of -0.17% (95%CI -0.44, 0.09). There was no heterogeneity between the studies.

Three recent RCTs were included in the evaluation as well, including 34 to 115 participants. Saslow et al.[14] evaluated very low carbohydrate diets, with a duration of 12 months. The RCT was not isocaloric and the comparator diet was defined as moderate carbohydrate, calorie restricted, low fat. The other two (Sato et al.[16] and Tay et al.[15] [2018]) evaluated low carbohydrate diets, with durations of 18 and 24 months, respectively. The RCT of Tay et al. (2018) was isocaloric, whereas the RCT of Sato et al. was not. Comparator diets were defined as high carbohydrate, low fat or calorie restricted. The RCT of Tay et al. (2018) was already included in the MA of Sainsbury et al., albeit with a shorter duration (12 months vs 24 months in the more recent RCT). At both time points, no difference in effect on HbA1c change was found. Also, Sato et al. found no differences in effects between advising low and high carbohydrate diets. In contrast, Saslow et al. found greater reductions in HbA1c among participants who were advised a very low carbohydrate diet than in the group who were advised a high carbohydrate diet. This may (among others) be explained by the relatively good compliance and retention rates. The study of Saslow et al. is relatively small in size, and therefore, this RCT is unlikely to have changed the overall MA conclusion of no effect.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in the MA of Sainsbury et al.[5]

Substitution of carbohydrates

The vast majority of included RCTs addressed substitution of carbohydrates by a combination of protein and fat, and therefore no subgroup analyses by protein or fat substitution were possible. The types of fat that were advised for substitution were predominantly MUFAs, sometimes combined with PUFA or SFA.

Retention rates

Retention rates in the RCTs included by Sainsbury et al.[5] ranged from 67 to 87% in the (very) low carbohydrate diet groups. In the high carbo-

hydrate diet groups, retention rates were overall comparable to the (very) low carbohydrate diet groups.

From the individual RCTs, Tay et al.[15] (2018) had particularly low retention rates (57% vs 49% in the low and high carbohydrate diet groups, respectively). The other two individual RCTs had retention rates of 82-87% in the (very) low carbohydrate diet groups, and 67-83 in the high carbohydrate diet group.

Risk of bias

None of the RCTs included in the MA of Sainsbury et al.[5] were scored as high risk of bias. Of the recent individual RCTs, the RCTs of Saslow et al.[14] and Tay et al.[15] (2018) were scored as low risk of bias, and the RCT of Sato et al.[16] as with *some concerns*.

Although none of the RCTs included by Sainsbury et al. was scored as high risk of bias, the RCT of Stern et al.[44] is worth noting due to relatively low retention rates (67% vs 59% in low vs high carbohydrate diet groups), and LOCF analyses performed for those who dropped out. However, given that the RCT contributed relatively little weight to the MA, no major impact on the MA result is expected.

Also, the recent RCT of Tay et al. (2018) is worth noting due to its low retention rates. Analyses were performed intention to treat (ITT), although it is unclear which data was used for those who dropped out. Therefore, the risk of incomplete outcome bias is unclear, as well as the impact on the RCT result.

The overall quality of the evidence was scored as low by Sainsbury et al. due to high risk of performance and detection bias, and inconsistency in the estimates of effect across studies.

Sainsbury et al. reported there was no publication bias present in the MA of combined low and moderate carbohydrate diet RCTs.

Dietary compliance

Regarding the RCTs included in the MA of Sainsbury et al.[5], the achieved intakes in the very low carbohydrate diet RCT were within the range of a low to moderate carbohydrate diet. Of the other 3 RCTs, which advised low carbohydrate diets, two reported achieved intakes at the level of moderate carbohydrate diets (Davis et al.[28]; Guldbrand et al.[45]), and one reported achieved intakes comparable to the prescribed intakes (Tay et al.[43] [2015]).

Regarding the individual RCTs, Tay et al.[15] (2018) showed rather comparable achieved and prescribed intakes of carbohydrates in the low carbohydrate diet groups. Saslow et al.[14] advised very low carbohydrate diets, whereas the intakes were within the range of a low carbohydrate

diet. In the individual RCT of Sato et al.[16], achieved intakes in the low carbohydrate diet group were within the range of a moderate carbohydrate diet. Moreover, in this RCT, achieved carbohydrate intakes were similar in the low and high carbohydrate groups (214 and 215 g/d, respectively).

To sum up, the vast majority of study participants were not able to comply with (very) low carbohydrate diets, and mainly achieved diets comparable to low (for very low carbohydrate diets) or moderate carbohydrate diets. This may have contributed to the lack of effect in the MA of Sainsbury et al.

Summary

The MA of Sainsbury et al.[5] did not find evidence for long term effects on HbA1c of advising (very) low compared with high carbohydrate diets, with no heterogeneity between studies. More recent RCTs generally support this finding. The included studies overall advised substituting the carbohydrates in the low carbohydrate diet with a combination of fat and protein. Some RCTs had moderate retention rates. However, due to the lack of heterogeneity between studies it is not expected to have impacted the conclusions. None of the included studies were at high risk of bias. Difficulties with long-term compliance regarding the (very) low carbohydrate diet may have contributed to the lack of effect.

Moderate carbohydrate diets

Study characteristics and main effects

One MA, of Sainsbury et al.[5], was included in the evaluation of moderate carbohydrate diets, covering 8 RCTs and 1,293 participants. One RCT had a duration of 9 months, 5 were of 12 months' duration, and the other two lasted for 16 and 24 months. The RCTs of Wolever et al.[26] and Krebs et al.[34] had the largest weight in the MA, followed by Larsen et al.[35] and Elhayany et al.[46].

In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. All but one (Wolever et al.) of the included RCTs were isocaloric. Comparator diets were often defined as high carbohydrate, low fat, and/or low protein diets. One (Elhayany et al.) defined two comparator diets, namely traditional Mediterranean, and according to diabetes association recommendations.

No difference in the effects of advising a moderate compared with high carbohydrate diet was found, with a WMD in HbA1c of 0.08% (95%CI -0.23, 0.06). There was moderate heterogeneity (I^2 30%) between studies, without further explanation by the authors. From comparing the effect estimates and confidence intervals of the RTCs, it can be concluded that the study of Fabricatore et al.[40] likely contributed to this heterogeneity. That study was of shorter duration than the other studies (9 months), the difference in achieved carbohydrate intakes between the moderate and

high carbohydrate group was relatively large (9 en%), and the RCT focused on a low glycaemic load in the moderate carbohydrate diet. Those factors may have contributed to the differences in effect compared with other studies.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in the MA of Sainsbury et al.[5]

Substitution of carbohydrates

Of the 8 RCTs included in the MA of Sainsbury et al.[5], 4 evaluated advised substitution of carbohydrates with protein and 4 with fat, of which 3 specified the type of fat as MUFAs. The types of protein were not specified. The effects on HbA1c change do not noticeably differ by type of substitution (Table 8).

Table 8 Long-term effects of advising moderate carbohydrate diets compared with high carbohydrate diets on HbA1c change (%): RCTs with substitutions for protein and fat.

RCT	Substitution	Mean difference (95%CI) in HbA1c change (%)
Brinkworth, 2004[47]	Protein	-0.30 (-0.96, 0.36)
Krebs, 2012[34]	Protein	-0.04 (-0.28, 0.20)
Larsen, 2011[35]	Protein	0.05 (-0.22, 0.32)
Pedersen, 2014[48]	Protein	0.00 (-0.52, 0.52)
Brehm, 2009[38]	Fat	-0.10 (-0.70, 0.50)
Elhayany, 2010[46]	Fat	-0.30 (-0.63, 0.03)
Fabricatore, 2011[40]	Fat	-0.70 (-1.25, -0.15)
Wolever, 2008[26]	Fat	0.06 (-0.13, 0.25)

CI: confidence interval; HbA1c: glycated haemoglobin; RCT: randomised controlled trial.

Retention rates

Retention rates ranged from 56 to 81% in the moderate carbohydrate diet groups, and 61 to 85% in the high carbohydrate diet groups. The RCTs of Fabricatore et al.[40] and Brinkworth et al.[47] had particularly low retention rates.

Risk of bias

The RCTs of Brinkworth et al.[47] and Wolever et al.[26] were scored as high risk of bias due to incomplete outcome data and completers-only analyses.

In the RCTs of Brinkworth et al, there was also an imbalanced baseline body weight between groups at 12 months. The domain “other bias” was

scored as unclear since Meadow Lea foods funded the study and the funders' involvement in the study was not specified. The RCT of Brinkworth et al. contributed only 3% weight to the MA.

The RCT of Wolever et al. was scored as high risk of bias due to incomplete outcome data. Data were reported for completers only. At 12 months follow-up, approximately 20% had dropped out in each group. Also, a high risk of other type of bias was detected since the first author is president and part-owner of GI Index Testing Inc. The RCT of Wolever et al. had a relatively high weight in the MA. Excluding the studies at high risk of bias did not noticeably change the MA result, with a WMD in HbA1c change of -0.13% (-0.30, 0.03), I^2 not reported. This suggests these RCTs did not impact the MA conclusion.

Even though the RCT of Fabricatore et al.[40] was not scored as high risk of bias, the RCT is worth mentioning due to the low retention rates. The RCT had a relatively low effect estimate and likely contributed to the heterogeneity between studies included in the MA. The authors argue that hierarchical linear modelling was used so that all participant data contributed to the analysis, thereby avoiding bias due to incomplete outcome data. In addition, the study had a relatively small weight in the MA, and likely did not noticeably impact the MA result.

The overall quality of the evidence was scored as low by Sainsbury et al.[5] due to high risk of performance and detection bias, and inconsistency in the estimates of the effect across studies.

Sainsbury et al. reported there was no publication bias present in the MA of combined low and moderate carbohydrate diet RCTs.

Dietary compliance

The RCT of Brinkworth et al.[47] did not report achieved intakes. For the remaining 7 RCTs included in the MA of Sainsbury et al.[5], achieved carbohydrate intakes in the moderate carbohydrate groups were overall slightly higher than prescribed. Nevertheless, intakes were within the range of moderate carbohydrate diets or slightly above (46 en%), suggesting compliance with the moderate carbohydrate diet was acceptable. Achieved intakes in the high carbohydrate groups were overall lower than prescribed. As a consequence, in half of the RCTs (Elhayany et al.[46], Krebs et al.[34], Larsen et al.[35], Pedersen et al.[48]), achieved carbohydrate intakes in the moderate carbohydrate diet groups differed only 2 to 6 en% from the achieved carbohydrate intakes in the high carbohydrate groups. Three of those had relatively large weights in the MA. In the remaining RCTs, it differed 8 to 13 en%. It can therefore be concluded that compliance with moderate carbohydrate diets was generally acceptable. However, differences between achieved intakes in moderate and high

carbohydrate diet advice groups were rather small in many of the RCTs. This may have contributed to the lack of effect found in the MA.

Summary

The MA of Sainsbury et al.[5] did not find evidence for long-term effects of advising moderate carbohydrate diets compared with high carbohydrate diets on HbA1c, with moderate heterogeneity between RCTs. There were no noticeable differences when the carbohydrates in the moderate carbohydrate diet were advised to be substituted by either fat or protein. Some RCTs had moderate retention rates, and two RCTs were at high risk of bias, among others due to incomplete outcome data. However, those RCTs did not noticeably affect the MA result. Compliance with moderate carbohydrate diets was generally acceptable. However, the rather small differences in achieved carbohydrate intakes between the moderate and high carbohydrate groups may have contributed to the lack of effect found in the MA.

3.3 Body weight

3.3.1 Short-term effects on body weight

Table 9 summarises the results and characteristics of the MAs that provided evidence regarding the effects of advising low and moderate carbohydrate diets on body weight in the short term. In addition, Table 10 summarises the results and characteristics of a recently published individual RCT regarding this topic. Details of RCTs included in the MAs and the individual RCT are provided in **Annex C**.

Table 9 Short-term effects of advising low and moderate carbohydrate diets on body weight in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Sainsbury, 2018[5]; 3 months	Sainsbury, 2018[5]; 6 months	McArdle, 2019[11]; 3 to 6 months	Sainsbury, 2018[5]; 3 months	Sainsbury, 2018[5]; 6 months
Category of carbohydrate restriction	Low carbohydrate diets	Low carbohydrate diets	Low carbohydrate diets	Moderate carbohydrate diets	Moderate carbohydrate diets
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: <26 en%; c: >45 en%	i: <26 en%; c: >45 en%	i: 10 to 26 en%; c: 'higher' (NR)	i: 26 to 45 en%; c: >45 en%	i: 26 to 45 en%; c: >45 en%
Number of studies; total number of participants	4 RCTs; 325, including 4 with pre-diabetes[b]	4 RCTs; 274	5 RCTs; 239	8 RCTs; 632	5 RCTs; 796, including 30 people with type 1 diabetes[3]
Heterogeneity	No: 0%	Moderate: 33%	Moderate: 24%	No: 0%	Moderate: 48%
Strength of the effect: WMD[a] (95%CI)	-2.47 kg (95%CI -3.33, -1.60)	-1.07 kg (95%CI -2.52, 0.37)	-0.43 kg (95%CI -0.74, -0.12)	0.14 kg (95%CI -0.30, 0.59)	0.29 kg (95%CI -0.60, 1.17)
Study population	People diagnosed with type 2 diabetes or pre-diabetes[b]; men and women; overweight and obese; diabetes medications[d]: oral agents, insulin; Europe, USA	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[d]: oral agents, insulin; Europe, USA, Japan	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[d]: oral agents, insulin; Europe, Japan	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[d]: oral agents, insulin, and none (diet only) in one RCT[e]; Europe, Canada, USA, Australia	People diagnosed with type 2 and type 1[c] diabetes; men and women; overweight and obese; diabetes medications[d]: oral agents, insulin; USA, Canada, Australia, New Zeeland

CI: confidence interval; RCT: randomised controlled trial; NR: not reported; USA: United States of America.

[a] WMD = Weighted mean difference in body weight change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;
[b] The RCT of Saslow et al.[24] included 34 participants of whom 4 had pre-diabetes and 30 type 2 diabetes;
[c] One RCT, of Stychar et al.[25], contributed people with type 1 diabetes. This RCT included 30 participants.
[d] Diabetes medications represent the types of medications that were used among the participants of the included RCTs (it does not mean that all participants in all included RCTs used those medications);
[e] One RCT of Wolever et al.[26] included participants that did not use any diabetes medications (oral agents or insulin).

Table 10 Short-term effects of advising low carbohydrate diets on weight in type 2 diabetes: individual RCTs.

RCT; Study duration	Struik, 2020[17]; 4 months
Category of carbohydrate restriction	Low carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 14 en%; c: 50 en%
Number of participants in intervention (i) and control (c) group	i: 41; c: 43
Strength of the effect: Mean difference (95%CI)	-0.9 kg; (95%CI NR; p-value value 0.40)
Study population	People diagnosed with type 2 diabetes; diabetes duration[a]: 7 years; men and women, BMI[a] 35 kg/m^2; diabetes medications[b]: oral agents, insulin; Australia

BMI: body mass index; CI: confidence interval; NR: not reported; RCT: randomised controlled trial.

[a] BMI and diabetes duration values represent the average n the study population;

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

The Committee concluded the following:

Low carbohydrate diets

Effects after 3-month follow-up: **Intervention studies show that advising low carbohydrate diets compared with diets high in carbohydrates reduces body weight by approximately 2.5 kg in people diagnosed with type 2 diabetes after 3 months. The evidence is strong.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 5 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong.
2. There is no obvious heterogeneity in direction between studies.
3. There is a statistically significant reducing effect in the MAs.
4. The Committee noted some studies had moderate retention rates, and one of the included RCTs was at high risk of bias (among others, due to the risk of incomplete outcome data). However, the Committee expects this is unlikely to have impacted the conclusions, given the lack of heterogeneity between studies. Based on this, the Committee concluded that there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that very low carbohydrate diet studies had low dietary compliance, and for low carbohydrate diet studies the compliance was variable. This may have attenuated the effect sizes of the evaluated RCTs. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the lower compliance can be seen as part of

the effect under evaluation and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Effects after 6 months follow-up: **Intervention studies show there is likely no difference in the effect of advising low carbohydrate diets compared with advising diets high in carbohydrates on body weight after 6 months, in people diagnosed with type 2 diabetes.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 8 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is no obvious heterogeneity in directions of effects.
3. There was no statistically significant effect in the MAs.
4. The Committee noted that some studies had moderate retention rates, and one of the included RCTs was at high risk of bias, among others due to incomplete outcome data. However, the Committee expects this is unlikely to have impacted the conclusions, due to the low weight of this RCT in the MA. Based on this, the Committee concluded that there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that very low carbohydrate diet studies had low dietary compliance, and for low carbohydrate diet studies the compliance was variable. This may have contributed to the lack of effect in the MA. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the lower compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

Intervention studies show there is likely no difference in the effects of advising moderate carbohydrate diets compared with advising

diets high in carbohydrates on body weight within 3 to 6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 12 RCTs, with more than 150 participants included in the evaluation.
2. There is no obvious heterogeneity in directions of effects between RCTs when discarding one RCT performed among people with type 1 diabetes (that RCT was rather small and is unlikely to have affected the MA conclusion).
3. There is no statistically significant effect in the MA.
4. The Committee noted that some studies had moderate retention rates, and four of the included RCTs were at high risk of bias, among others due to incomplete outcome data. However, the Committee expects this is unlikely to have impacted the conclusions since there was no heterogeneity between studies. Based on this, the Committee concluded that there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake. Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that compliance with the moderate carbohydrate diets was good overall and is therefore unlikely to have contributed to the lack of effect.

Regarding substitution effects: The effects of advising moderate carbohydrate diets compared with high carbohydrate diets do not noticeably differ when it is advised to substitute the carbohydrates in the moderate carbohydrate diet with either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

Two MAs, of Sainsbury et al.[5] and McArdle et al.[11] were included in the evaluation of low carbohydrate diets. Those MAs included the same RCTs as used for the evaluation of short-term effects on HbA1c, except that the RCT of Samaha et al.[32] was not included in the 6-month analyses of Sainsbury et al. Details on study characteristics can be found in Section 3.2.1.

With respect to advising low carbohydrate diets, the MA of Sainsbury et al. found statistically significantly greater reductions in body weight compared with advising high carbohydrate diets at 3 months, but not at 6 months (WMD -2.47 kg (95%CI -3.33, -1.60) and -1.07 kg (95%CI -2.52, 0.37), respectively). There was no heterogeneity at 3 months and moderate

heterogeneity at 6 months, without further explanation by the authors. The MA of McArdle et al. found statistically significant greater reductions in body weight compared with advising high carbohydrate diets with RCTs of 3 to 6 months durations (WMD -0.43 kg (95%CI -0.74, -0.12)). This result was largely driven by the RCT of Daly et al.[27], which had a duration of 3 months. Therefore, it can be concluded that the MA results are in line with each other.

One recent RCT, of Struik et al.[17], was additionally included in the evaluation of low carbohydrate diets. The study lasted for 4 months, and was therefore taken into additional consideration for the 3-month effects (comparable to the approach used by Sainsbury et al.). The study included 84 participants, was isocaloric, and the comparator diet was defined as a high carbohydrate, low fat diet. Struik et al. showed a non-significant reducing effect on body weight in the group who were advised a low carbohydrate diet compared with the control group. This direction of effect is in line with the 3-month findings of the MA of Sainsbury et al.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in both MAs.[5,11]

Substitution of carbohydrates

In all RCTs, carbohydrates in the low carbohydrate diet were advised to be substituted by a combination of fat and protein. Subgroup analyses by protein or fat substitution were therefore not possible. In most RCTs, the types of fat that were advised as a substitution for the carbohydrates were not specified. Where specified, it was a combination of MUFA and PUFA or a combination of MUFA and SFA.

Retention rates

Retention rates ranged from 55 to 100% in the (very) low carbohydrate diet groups, and 63 to 100% in the control groups in the RCTs included by Sainsbury et al.[5] RCTs included by McArdle et al.[11] had retention rates that ranged from 78 to 100% in the low carbohydrate diet groups, and 76 to 100% in the control groups.

Risk of bias

Regarding the topic of risk of bias, descriptions are given in Section 3.2.1. In sum, it was explained that one RCT in the MA of Sainsbury et al.[5], of Westman et al.[31] (contributing to both 3 and 6-month analyses), was scored as high risk of bias, among others due to incomplete outcome data. The RCT of Westman et al. likely contributed to some extent to the

heterogeneity between studies at 6 months. No sensitivity analyses excluding studies at high risk of bias were performed. However, that RCT is unlikely to have noticeably affected the MA conclusions due to lack of heterogeneity at 3 months and due to the minor weight in the MA at 6 months.

None of the RCTs in the MA of McArdle et al.[11] was scored as high risk of bias.

The individual RCT of Struik et al.[17] was judged as low risk of bias.

Compliance

Regarding the topic of compliance, descriptions are given in Section 3.2.1. It was concluded that very low carbohydrate diets were difficult to comply with for the study participants and that compliance with low carbohydrate diets varied in both MAs. The effect sizes presented in the MAs may have been attenuated by the relatively low compliance, and issues with compliance can have contributed to the lack of effect in the 6-month MA.

Summary

The MAs of Sainsbury et al.[5] and McArdle et al.[11] suggest there are greater reductions in body weight when (very) low carbohydrate diets are advised compared with high carbohydrate diets after 3 months follow-up, but not after 6 months. Some of the RCTs included by Sainsbury et al. and McArdle et al. had moderate retention rates, and one RCT included by Sainsbury et al. had a high risk of bias, among others due to incomplete outcome data. However, that RCT is unlikely to have affected the MA conclusions due to lack of heterogeneity at 3 months and due to the minor weight in the MA at 6 months. Compliance with very low carbohydrate diets was rather low, and variable for low carbohydrate diets. This may have contributed to the lack of effect at 6 months.

Moderate carbohydrate diets

Study characteristics and main effects

One MA, of Sainsbury et al.[5], was included in the evaluation of the effects of advising a moderate carbohydrate diet. This MA included the same RCTs as used for the evaluation of short-term effects on HbA1c, except that the RCT of Fabricatore et al.[40] was not included in the 6-month analyses. Details on study characteristics can be found in Section 3.2.1. One of the RCTs, of Stychar et al.[25], was performed among people with type 1 diabetes. Unfortunately, no analyses for the body weight outcome excluding the RCT of Stychar et al. were available. The study included only 30 participants, and contributed 12% weight to the MA.

No effects of advising moderate carbohydrate diets were found on weight change, compared with advising high carbohydrate diets, with WMD of 0.14 kg (95%CI -0.30, 0.59) and 0.29 kg (95%CI -0.60, 1.17), after 3 and 6 months respectively. There was no heterogeneity at 3 months and

moderate heterogeneity at 6 months. Heterogeneity at 6 months was likely due to the RCT of Stycher et al., which was performed among people with type 1 diabetes. The Committee expected that the MA conclusion of no effect would not have changed if the RCT of Stychar et al. had been excluded.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in the MA of Sainsbury et al.[5]

Substitution of carbohydrates

In 4 RCTs, carbohydrates in the moderate carbohydrate diets were advised to be substituted by protein, and in 3 RCTs by fat, predominantly MUFAs. The types of protein were not specified. For two RCTs, carbohydrates were advised to be substituted by a combination of fat and protein. No noticeable differences were observed with substitutions by protein versus fat (Table 11). In the RCTs with fat substitutions, the advised substituted fats were MUFAs combined with either PUFA or SFA. The RCT of Stychar et al.[25] was not taken into account given the study population of people with type 1 diabetes.

Table 11 Short-term effects of advising moderate carbohydrate diets compared with high carbohydrate diets on body weight change (kg): RCTs with substitutions for protein, fat or a combination of protein and fat.

RCT	Substitution(s)	Mean difference (95%CI) in weight change (kg)
Krebs, 2012[34]	Protein	-0.08 (-1.02, 0.86)
Larsen, 2011[35]	Protein	0.29 (-0.61, 1.19)
Luger, 2013[36]	Protein	-2.10 (-5.16, 0.96)
Parker, 2002[37]	Protein	-0.70 (-2.18, 0.78)
Brehm, 2009[38]	Fat	3m: -0.60 (-2.51, 1.31); 6m: -0.60 (-2.55, 1.35)
Brunerova, 2007[39]	Fat	-0.80 (-3.60, 2.00)
Wolever, 2008[26]	Fat	3m: 0.50 (-0.12, 1.12); 6m: 0.20 (-0.61, 1.01)
Watson, 2016[41]	Fat & protein	3m: -0.40 (-2.61, 1.81); 6m: -1.20 (-4.81, 2.41)
Wycherley, 2010[42]	Fat & protein	-0.40 (-3.93, 3.13)

CI: confidence interval; kg: kilograms; m: months; RCT: randomised controlled trial.

Retention rates

For the studies that reported retention rates at 3 or 6 months, the majority of RCTs reported retention rates of 82% or higher, except two RCTs (Wycherley et al.[42] and Watson et al.[41]), that reported retention rates of 57% (moderate carbohydrate diet group) and 72% (both intervention and control group). Both RCTs had relatively little weight in the MA and this is unlikely to have affected the MA result.

Risk of bias

Regarding the topic of risk of bias, descriptions are given in Section 3.2.1. The RCTs of Brunerova et al.[39], Parker et al.[37], Wolever et al.[26], and Stychar et al.[25] were scored as high risk of bias. The study of Stychar et al. caused heterogeneity in the 6-month MA. However, due to the small number of participants included in this RCT, it is not expected this RCT affected the MA conclusion of no difference in effect. Due to the lack of heterogeneity between the remaining studies, the other RCTs at high risk of bias are unlikely to have affected the MA results.

Dietary compliance

Regarding the topic of compliance, descriptions are given in Section 3.2.1. It was concluded that participants were overall compliant with the study diets.

Summary

The MA of Sainsbury et al.[5] did not find differences in short-term effects on body weight for advising moderate compared with high carbohydrate diets, and when discarding the RCT of Stychar et al.[25] that was performed in people with type 1 diabetes, there was no noticeable heterogeneity between studies. Some studies had moderate retention rates, and four RCTs were at high risk of bias, among others, due to incomplete outcome data. Those RCTs are unlikely to have affected the MA results since no heterogeneity between studies was present. There was good compliance with the moderate carbohydrate diets.

3.3.2 Longer-term effects on body weight

Table 12 summarises the results and characteristics of the MA that provided evidence regarding the effects of advising low and moderate carbohydrate diets on body weight in the longer term. In addition, Table 13 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MA and the individual RCTs are provided in **Annex D**.

Table 12 Long-term effects of advising low and moderate carbohydrate diets on body weight in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Sainsbury, 2018[5]; 12 months	Sainsbury, 2018[5]; 9 to 12 months
Category of carbohydrate restriction	Low carbohydrate diets	Moderate carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: <26 en%; c: >45 en%	i: 26 to 45 en%; c: >45 en%
Number of studies; total number of participants	3 RCTs; 281	7 RCTs; 1211
Heterogeneity	No: 0%	No: 0%
Strength of the effect: WMD[a] (95%CI)	0.58 kg (95%CI -0.83, 1.99)	-0.58 kg (95%CI -1.11, -0.04)
Study population	People diagnosed with type 2 diabetes; men and women; diabetes medications[b]: oral agents, insulin; Europe, USA, Australia	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[b]: oral agents, insulin, and none (diet only) in one RCT[c]. USA, Australia, Asia, New Zeeland

CI: confidence interval; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean difference in body weight change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] Diabetes medications represent the types of medications that were used among the participants of the included RCTs (it does not mean that *all* participants in all included RCTs used those medications);

[c] One RCT of Wolever et al.26 included participants that did not use any diabetes medications (oral agents or insulin).

Table 13 Long-term effects of advising low carbohydrate diets on body weight in people with type 2 diabetes: individual RCTs.

RCT; Study duration	Saslow, 2017[14]; 12 months	Sato, 2017[16]; 18 months	Tay, 2018[15]; 24 months
Category of carbohydrate restriction	Very low carbohydrate diet	Low carbohydrate diet	Low carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 20 to 50 g; c: 45 to 50 en%	i: 130 g; c: 50 to 60 en%	i: 14 en%; c: 53 en%
Number of participants in intervention (i) and control (c) group	i: 16; c: 18	i: 33; c: 33	i: 58; c: 57
Strength of the effect: Mean difference (95%CI)[a]	-6.2 kg; 95%CI: NR; p-value <0.001[b]	-0.9 kg; 95%CI: NR; p-value 0.64[c]	-0.1 kg (95%CI: -3.1, 2.8)[b]
Study population	People diagnosed with type 2 diabetes or pre-diabetes; diabetes duration[d]: 7 years; men and women; BMI[d]: 37 kg/m^2; diabetes medications[e]: oral agents; USA	People diagnosed with type 2 diabetes; diabetes duration: 13 (i) and 14 (c) years; men and women; BMI[d]: 27 kg/m^2; diabetes medications[e]: oral agents, insulin; Japan	People diagnosed with type 2 diabetes; diabetes duration: 7 years; men and women; BMI[d]: 35 kg/m^2; diabetes medications[e]: oral agents insulin; Australia

BMI: body mass index; CI: confidence interval; NR: not reported; RCT: randomised controlled trial; USA: United States of America.

[a] Values are the differences in estimated marginal mean changes between low and high carbohydrate diet groups;

[b] Derived from mixed effects linear regression model;

[c] p-values were derived from Mann-Whitney U test;

[d] BMI and diabetes duration values represent the average in the study population;

[e] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

The Committee concluded the following:

Low carbohydrate diets

Intervention studies show there is likely no difference in the effect of advising low carbohydrate diets compared with diets high in carbohydrates on body weight within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 6 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is no obvious heterogeneity in direction of effects between studies.
3. There is no statistically significant effect in the MA, and this is overall supported by recent RCTs.
4. The Committee noted that some studies had moderate retention rates. However, the Committee expects this is unlikely to have impacted the conclusions since there was no heterogeneity between studies. Also, the study with the lowest retention rates had a minor weight in the MA. Based on this, the Committee drew conclusions and there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that compliance with the (very) low carbohydrate diets was overall poor. This may (partly) explain the lack of effect found in the MA. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the poor compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

Intervention studies show that advising moderate carbohydrate diets compared with diets high in carbohydrates reduces body weight by approximately 0.6 kg in people diagnosed with type 2 diabetes within 9 to 12 months. The evidence is limited.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 7 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong. However, there were other considerations that led to the conclusion of limited evidence, as described below (point 4).
2. There is no obvious heterogeneity in direction of effects between studies.
3. There was a small yet statistically significant reducing effect in the MA.
4. Despite the lack of heterogeneity between studies, the Committee noted that one RCT at high risk of bias and with a large weight in the MA may have contributed to a large extent to the statistical significance of the overall MA result. This reduces the certainty of the MA conclusion. Based on this, the Committee concluded that the evidence is limited (instead of strong).

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that contrasts in achieved intakes of carbohydrates between the intervention and control groups were small. This may have attenuated effect sizes found in the RCTs. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: Effects of advising moderate carbohydrate diets compared with high carbohydrate diets do not noticeably differ when it is advised to substitute the carbohydrates in the moderate carbohydrate diet by either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

The MA of Sainsbury et al.[5] was included in the evaluation of low carbohydrate diets. This MA included the same RCTs as used for the longer-term effects on HbA1c, except that the RCT of Stern et al.[44] was not included in the analyses. All included RCTs evaluated low carbohydrate diets (i.e. non-evaluated very low carbohydrate diets). Details on study characteristics can be found in Section 3.2.2.

No effect of advising low carbohydrate diets compared with high carbohydrate diets on body weight change was found, with a WMD of 0.58 kg (95%CI -0.83, 1.99). There was no heterogeneity between studies.

Three recent RCTs were included in the evaluation as well. Saslow et al.[14] evaluated very low carbohydrate diets. The other two (Sato et al.[16] and Tay et al.[15]) evaluated low carbohydrate diets. Further details of those RCTs are described in Section 3.2.2. The RCTs of Tay et al. and Sato et al. found no differences in effects on body weight between advising low and high carbohydrate diets. Contrarily, Saslow et al. found greater reductions in body weight among participants in the group that was advised a very low carbohydrate diet than in the group that was advised a high carbohydrate diet. This may be explained by the relatively good compliance and retention rates. The study is relatively small in size and it is therefore unlikely that this RCT would change the overall MA conclusion of no effect.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in the MA of Sainsbury et al.[5]

Substitution of carbohydrates

In all RCTs, carbohydrates in the low carbohydrate diet were advised to be substituted by a combination of fat and protein. Subgroup analyses by protein or fat substitution were therefore not possible. The types of fat that were advised for the substitution were predominantly MUFAs, sometimes combined with PUFA or SFA.

Retention rates

Retention rates are described in Section 3.2.2. In sum, some studies had moderate retention rates. However, due to the lack of heterogeneity between studies, it is not expected that they impacted the overall conclusion.

Risk of bias

Regarding the topic of risk of bias, descriptions are given in Section 3.2.2. In summary, none of the RCTs included in the MA of Sainsbury et al.[5] were scored as high risk of bias. Of the recent, individual RCTs, the RCTs of Saslow et al.[14] and Tay et al.[15] were scored as low risk of bias. The RCT of Sato et al.[16] was scored as *some concerns*.

Dietary compliance

Regarding the topic of compliance, descriptions are given in Section 3.2.2. In summary, it was concluded that the vast majority of study participants were not able to comply with (very) low carbohydrate diets, and mainly achieved diets comparable to low (for very low carbohydrate diets) or moderate carbohydrate diets. This may have contributed to the lack of effect in the MA.

Summary

The MA of Sainsbury et al.[5] did not find evidence for long-term effects on body weight of advising diets low in carbohydrates compared with diets high in carbohydrates, with no heterogeneity between studies. More recent RCTs generally support this finding. Due to the lack of heterogeneity, the Committee does not expect moderate retention rates in some studies to have impacted the conclusion. Difficulties with long-term compliance regarding the low carbohydrate diet may have contributed to the lack of effect.

Moderate carbohydrate diets

Study characteristics and main effects

The MA of Sainsbury et al.[5] was included in the evaluation of moderate carbohydrate diets. This MA included the same RCTs as used for the longer-term effects on HbA1c, except that the RCT of Fabricatore et al.[40] was not included the analyses. Details on study characteristics can be found in Section 3.2.2.

A greater reduction in body weight was found for advising a moderate compared with high carbohydrate diet, with a WMD of -0.58 kg (95%CI -1.11, -0.04) body weight. There was no heterogeneity between studies.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed in the MA of Sainsbury et al.[5]

Substitution of carbohydrates

Of the 7 RCTs included in the MA of Sainsbury et al.[5], 4 evaluated RCTs advised substitution of carbohydrates with protein and 3 with fat, of which all 3 specified the type of fat as MUFAs. The types of protein were not specified. The effects on body weight change do not noticeably differ by type of advised substitution (Table 14).

Table 14 Long-term effects of advising moderate carbohydrate diets compared with high carbohydrate diets on body weight change (kg): RCTs with substitutions for protein and fat.

RCT	Substitution	Mean difference (95%CI) in weight change (kg)
Brinkworth, 2004[47]	Protein	-1.50 (-4.43, 1.43)
Krebs, 2012[34]	Protein	-0.56 (-2.07, 0.95)
Larsen, 2011[35]	Protein	-0.06 (-1.16, 1.04)
Pedersen, 2014[48]	Protein	-2.10 (-4.91, 0.71)
Brehm, 2009[38]	Fat	-0.20 (-2.14, 1.74)
Elhayany, 2010[46]	Fat	-1.40 (-2.51, -0.29)
Wolever, 2008[26]	Fat	-0.08 (-1.15, 0.99)

CI: confidence interval; kg: kilograms; RCT: randomised controlled trial.

Retention rates

Retention rates ranged from 56 to 81% in the moderate carbohydrate diet groups, and 61 to 85% in the high carbohydrate diet groups.

Risk of bias

Regarding the topic of risk of bias, descriptions are given in Section 3.2.2. In summary, two RCTs were scored as high risk of bias. However, due to lack of heterogeneity between studies, it is not expected those RCTs affected the overall MA conclusion. However, the RCT of Elhayany et al.[46] is important to note. That RCT likely contributed to a large extent to the overall MA result since it had a high weight in the MA. Although Sainsbury et al.[5] did not score this RCT as high risk of bias, the combination of moderate retention rates and per protocol analyses likely puts this study at high risk of bias due to incomplete outcome data, as acknowledged in risk of bias assessments in other MAs (Annex K). No sensitivity analyses, excluding the RCT of Elhayany et al., have been performed. Given the relatively strong inverse effect and large weight in the MA of this RCT, it reduces the certainty of the MA findings.

Dietary compliance

Regarding the topic of compliance, descriptions are given in Section 3.2.2. It was concluded that compliance with moderate carbohydrate diets is generally good. However, differences between achieved intakes in moderate and high carbohydrate diet groups were rather small in many of the RCTs. This may have contributed to an attenuated effect size of the MA result.

Summary

The MA of Sainsbury et al.[5] did find evidence for long-term body weight reductions when advising moderate carbohydrate diets compared with high carbohydrate diets, without heterogeneity between RCTs. However, incomplete outcome data in one of the RCTs that contributed largely to the overall MA conclusion reduces the certainty of the MA conclusion. Compliance with moderate carbohydrate diets was generally acceptable. However, differences in achieved carbohydrate intakes between groups advised moderate and high carbohydrate diets were rather small and this may have attenuated the MA result.

3.4 Fasting plasma glucose

3.4.1 Short-term effects on fasting plasma glucose

Tables 15 and 15a summarise the results and characteristics of the MA, and RCTs included in the MA, that provided evidence regarding the effects of advising low and moderate carbohydrate diets on fasting plasma glucose in the short term. In addition, Table 16 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MA and the individual RCTs are provided in **Annex E**.

Table 15 Short-term effects of advising low and moderate carbohydrate diets on fasting plasma glucose in type 2 diabetes: meta-analysis of RCTs.

Meta-analysis; Study duration	van Zuuren, 2018[10]; 4 to 6 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤40 en%; c: >40 en%
Number of studies; total number of participants	5 RCTs; 365
Number of studies according to category of carbohydrate restriction	Very low: 1; Low: 3; Moderate: 1
Heterogeneity	Yes: 67%
Strength of the effect: WMD[a] (95%CI)	Effect estimates per RCT included in the MA are shown in Table 15a[b]
Study population	People diagnosed with type 2 diabetes; men and women; where specified BMI varied between 33 and 50 kg/m^2; diabetes medications[c]: oral agents, insulin; Europe, Japan, Australia, Israel

BMI: body mass index; CI: confidence interval; MA: meta-analysis; RCT: randomised controlled trial.

[a] WMD = Weighted mean difference in fasting plasma glucose change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] No pooled effect estimate is presented in the current background document since the studies included in the MA were heterogeneous and combined low and moderate carbohydrate diets. Therefore, the Committee evaluated the evidence on RCT level, to allow separate conclusions on effects of advising low and moderate carbohydrate diets;

[c] Diabetes medications represent the types of medications that were used among the participants of the included RCTs (it does not mean that *all* participants in all included RCTs used those medications).

Table 15a Short-term effects of low and moderate carbohydrate diets on fasting plasma glucose in RCTs included in the meta-analysis of van Zuuren et al.[10]

RCT	Number of participants	Category of carbohydrate restriction	Effect (95%CI), mmol/L
Goday, 2016[49]	89	Low carbohydrate diet	-0.60 (-1.18, -0.02)
Shai, 2008[50]	23	Low carbohydrate diet	-0.70 (-1.07, -0.33)
Tay, 2014[51]	93	Low carbohydrate diet	0.50 (-0.46, 1.46)
Yamada, 2014[52]	24	Low carbohydrate diet	-1.22 (-2.54, 0.10)
De Bont, 1981[53]	136	Moderate carbohydrate diet	-0.20 (-0.32, -0.08)

CI: confidence interval; RCT: randomised controlled trial.

Table 16 Short-term effects of advising moderate carbohydrate diets on fasting plasma glucose in type 2 diabetes: individual RCTs.

RCT; Study duration	Liu, 2018[12]; 3 months	Wang, 2018[13]; 3 months
Category of carbohydrate restriction	Moderate carbohydrate diet	Moderate carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 42 en%; c: 54 en%	i: <45 en%; c: NR
Number of participants in intervention (i) and control (c) group	i: 30; c: 30	i: 28; c: 28
Strength of the effect: Mean difference (95%CI)	-0.65 (-1.21, -0.09) mmol/L[a]	0.17 mmol/L: (95%CI NR; p-value from t-test: >0.05)
Study population	People newly diagnosed with type 2 diabetes; men and women; BMI[b]: 24 kg/m^2 (i) and 25 kg/m^2 (c); diabetes medications[c]: none (diet only); China (Asia)	People diagnosed with type 2 diabetes; diabetes duration[b]: 13 (i) and 9 (c) years; men and women; BMI[b]: 22 kg/m^2 (i) and 21 kg/m^2 (c); diabetes medications[c]: oral agents, insulin; China (Asia)

BMI: body mass index; CI: confidence interval; NR: not reported; RCT: randomised controlled trial.

[a] The outcome is serum glucose instead of plasma glucose;
[b] BMI and diabetes duration values represent the average in the study population;
[c] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

The Committee concluded the following:

Low carbohydrate diets
Intervention studies show that advising low carbohydrate diets compared with advising diets high in carbohydrates reduces fasting plasma glucose within 4 to 6 months, in people diagnosed with type 2 diabetes. The evidence is limited.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There is no MA that addresses the effect of advising low carbohydrate diets separately from moderate carbohydrate diets. There are 4 individual RCTs with more than 90 participants, which excludes a conclusion with strong evidence.
2. There is moderate heterogeneity in the direction of the effects of RCTs, with three showing (almost) statistically significant reducing effects of low carbohydrate diets, and one showing no effect. In the study that showed no effect, other parameters of glycaemic control, including HbA1c, decreased during the intervention. It is unclear why a similar decrease in fasting glucose was not observed.
3. The Committee noted that some of the included studies had moderate retention rates. However, the Committee expects this is unlikely to have impacted the overall conclusion since there was only moderate heterogeneity between studies. Moreover, in the study with the lowest

retention rates, those rates were based on the retention at 24 months, and it is expected that the short-term retention was higher. Based on this, the Committee concluded that there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that compliance with the very low carbohydrate diet was unknown, and variable for the low carbohydrate diets. This may have attenuated the effect sizes of the evaluated RCTs. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the lower compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising moderate carbohydrates diets compared with advising diets high in carbohydrates on fasting plasma glucose within 3 to 6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There is no MA that addresses the effect of advising moderate carbohydrate diets separately from low carbohydrate diets. There are 3 individual RCTs, with more than 90 participants, which excludes a conclusion with strong evidence.
2. There is moderate heterogeneity in effects between the RCTs that addressed moderate carbohydrate diets, with two showing statistically significant reducing effects of advising moderate carbohydrate diets, and one showing no effect. It is unclear what causes this heterogeneity. Therefore, the Committee concluded the evidence is inconclusive. With only 3 RCTs contributing to the evidence, inconclusive evidence leads to the conclusion of too little evidence.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that, where reported, compliance with the moderate carbohydrate diets was good overall and therefore unlikely to have contributed to the heterogeneity in effects.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

No MAs that addressed the effects of advising low carbohydrate diets on fasting plasma glucose were available. Therefore, 4 RCTs, focussing on low carbohydrate diets, that contributed to the MA of van Zuuren et al.[10] were evaluated (see Table 15a). Study durations ranged from 4 to 6 months. Of the 4 RCTs included in the MA, 1 was a very low, and 3 were low carbohydrate diet interventions. The RCTs of Goday et al.[49] and Tay et al.[51] had the largest number of participants.

In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. One RCT (Tay et al.) was isocaloric, whereas the others were not. In the non-isocaloric studies, the intervention group was often prescribed a carbohydrate restriction and the control group a calorie restriction. Comparator diets were defined as high carbohydrate, calorie restricted, and/or low fat.

There was moderate heterogeneity in the effects reported by the 4 RCTs, with three reporting (nearly) statistically significant reducing effects on fasting plasma glucose and one (Tay et al.) reporting no effect. More specifically, fasting plasma glucose decreased in both the intervention and control group, without differences between the groups in the study of Tay et al. Other parameters of glycaemic control: HbA1c and glycaemic variability (amplitude, frequency, and duration of diurnal glucose fluctuations) did improve in the intervention compared with the control group in the study of Tay et al. Van Zuuren et al. note that it remains unclear why the study of Tay et al. caused heterogeneity.

Substitution by protein or fat

In all RCTs, it was advised to substitute the carbohydrates in the low carbohydrate diet with a combination of protein and fat, or the substituting macronutrients were unspecified. Subgroup analyses by protein or fat substitution were therefore not possible. Where specified, the types of fat in the substitution were (M)UFAs.

Retention rates

The retention rates ranged from 63 to 100% in the low carbohydrate diet groups and 82 to 100% in the high carbohydrate diet groups. The RCT of Shai et al.[50] is worth noting since this RCT had the highest drop-out rates and a higher drop out in low carbohydrate diet group (37%) than the high carbohydrate diet group (8%). However, drop-out rates for the RCT of Shai et al. were based on 24-month data and it is unknown if such imbalances were also present in the short term (6 months). Given that the study findings of Shai et al. are in line with the majority of other RCTs, and, in general, retention rates in the shorter term are higher than in the longer term, it is not expected to have majorly impacted the 6-month findings of Shai et al.

Risk of bias

All RCTs were scored as unclear risk of bias by van Zuuren et al.[10]
Van Zuuren et al. reported the overall quality for combined low and moderate carbohydrate diets of the evidence regarding fasting plasma glucose at 16-26 weeks. It was graded as moderate, particularly due to inconsistency in the findings.

Publication bias

Van Zuuren et al.[10] did not assess publication bias because there were too few studies that evaluated the effect on fasting plasma glucose at the same specific time points.

Dietary compliance

Compliance with the very low carbohydrate diet (Goday et al.[49]) was not reported. For the low carbohydrate diets, achieved intakes were in line with those prescribed for two RCTs (Tay et al.[51] and Yamada et al.[52]).
For the study of Shai et al.[50], achieved intakes in en% were higher than the cut off for low carbohydrate diets, and this may to some extent have contributed to attenuation of the reported effect. It should, however, be noted that the reported achieved intakes by Shai et al. were for the full study population whereas for the current evaluation, a selection of that study population, namely only those with type 2 diabetes, was used. The achieved intakes for people with type 2 diabetes are unknown.

Summary

Of four RCTs included in the MA of van Zuuren et al.[10], three RCTs showed reducing effects on fasting plasma glucose with advising (very) low carbohydrate diets compared with high carbohydrate diets. One RCT showed no differences in effects. None of the RCTs were judged as high risk of bias. Some of the RCTs had moderate retention rates.
The Committee expects this is unlikely to have impacted the overall conclusion since there was only moderate heterogeneity between studies. Moreover, in the study with the lowest retention rates, those rates were based on the retention at 24 months, and it is expected that the short-term retention was higher. Compliance with the low carbohydrate diets was variable, and unclear for the very low carbohydrate diet.

Moderate carbohydrate diets

Study characteristics and main effects

No MAs that addressed the effect of advising moderate carbohydrate diets were available. Therefore, the Committee evaluated three single RCTs. One RCT, of de Bont et al.[53], was part of the main MA of van Zuuren et al.[10] (see Table 15a). That study lasted for 6 months. Furthermore, two recently published RCTs, of Liu et al.[12] and Wang et al.[13], contributed to the evaluation of effects of advising moderate carbohydrate diets. Both lasted for 3 months. The RCT of Liu et al. was isocaloric whereas the other two RCTs were not. Comparator diets were defined as high carbohydrate and/or low fat diets.

De Bont et al. and Liu et al. found that advising moderate carbohydrate diets lowered fasting plasma glucose compared with advising high carbohydrate diets, whereas Wang et al. found no differences in effect. It is unclear what caused these differences.

Substitution by protein or fat

There were too few studies to evaluate potential differences in effects when the carbohydrates in the moderate carbohydrate diets were advised to be substituted by either fat or protein. Two RCTs evaluated advised substitutions of carbohydrates with fat, of which one specified the types of fat, which were predominantly SFA and MUFA. One RCT evaluated advised substitutions with protein.

Retention rates, risk of bias and compliance

Retention rates ranged from 83 to 92%. None of the studies were judged as high risk of bias. Reported intakes in the moderate carbohydrate diet groups were in line with what was prescribed. Those factors unlikely biased the effects reported in the RCTs.

Van Zuuren et al.[10] reported the overall quality for combined low and moderate carbohydrate diets of the evidence regarding fasting plasma glucose at 16-26 weeks. It was graded as moderate, particularly due to inconsistency in the findings.

Publication bias

Van Zuuren et al.[10] did not assess publication bias because there were too few studies that evaluated the effect on fasting plasma glucose at the same specific time points.

Summary

Three RCTs evaluated the effects of advising moderate carbohydrate diets on fasting plasma glucose, compared with advising high carbohydrate diets. One found no effect whereas the other two found reducing effects on fasting plasma glucose. None of the RCTs was judged as high risk of bias. The compliance with the moderate carbohydrate diets was good.

3.4.2 Longer-term effects on fasting plasma glucose

Tables 17 and 17a summarise the results and characteristics of the MA, and RCTs included in the MA, that provided evidence regarding the effects of advising low and moderate carbohydrate diets on fasting plasma glucose in the longer term. In addition, Table 18 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MA and the individual RCTs are provided in **Annex F**.

Table 17 Long-term effects of advising low and moderate carbohydrate diets on fasting plasma glucose in people with type 2 diabetes: meta-analysis of RCTs.

Meta-analysis; Study duration	Van Zuuren, 2018[10]; 12 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤40 en%; c: >40 en%
Number of studies; total number of participants	4 RCTs; 340
Number of studies according to category of carbohydrate restriction	Very low: 0; Low: 1; Moderate: 3
Heterogeneity	Yes: 92%
Strength of the effect: WMD[a] (95%CI)	Effect estimates per RCT included in the MA are shown in Table 17a[b]
Study population	People diagnosed with type 2 diabetes; men and women; where specified, the average BMI was 31 kg/m^2; diabetes medications[c]: oral agents, and none in two RCTs[d]; Europe, Canada, Israel

BMI: body mass index; CI: confidence interval; MA: meta-analysis; RCT: randomised controlled trial.

[a] WMD = Weighted mean difference in fasting plasma glucose change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] No pooled effect estimate is presented in the current background document since the studies included in the MA were heterogeneous and combined low and moderate carbohydrate diets. Therefore, the Committee evaluated the evidence on RCT level, to allow separate conclusions on effects of advising low and moderate carbohydrate diets.

[c] Diabetes medications represent the types of medications that were used among the participants of the included RCTs (it does not mean that all participants in all included RCTs used those medications);

[d] Two RCTs, of Wolever et al.[26] and Hockaday et al.[54], included participants that did not use any diabetes medications (oral agents or insulin).

Table 17a Long-term effects of low and moderate carbohydrate diets on fasting plasma glucose in RCTs included in the meta-analysis of van Zuuren et al.[10]

RCT	Number of participants	Category of carbohydrate restriction	Effect (95%CI), mmol/L
Shai, 2008[50]	23	Low carbohydrate diet	-1.17 (-1.62, -0.72)
Elhayany, 2010[46]	116	Moderate carbohydrate diet	-1.22 (-1.68, -0.76)
Hockaday, 1978[54]	93	Moderate carbohydrate diet	1.50 (0.40, 2.60)
Wolever, 2008[26]	108	Moderate carbohydrate diet	-0.10 (-0.39, 0.19)

CI: confidence interval; RCT: randomised controlled trial.

Table 18 Long-term effects of advising low carbohydrate diets on fasting plasma glucose in people with type 2 diabetes: individual RCT.

RCT; Study duration	Tay, 2018[15]; 24 months
Category of carbohydrate restriction	Low carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 14 en%; c: 53 en%
Number of participants in intervention (i) and control (c) group	i: 58; c: 57
Strength of the effect: Mean difference (95%CI)	0.7 (-0.3, 1.7) mmol/L[a]
Study population	People diagnosed with type 2 diabetes; diabetes duration[b]: 7 years; men and women; BMI[b]: 35 kg/m^2; diabetes medications[c]: oral agents insulin; Australia

BMI: body mass index; CI: confidence interval; RCT: randomised controlled trial.

[a] Value is the differences in estimated marginal mean changes between low and high carbohydrate diet group, derived from mixed effects linear regression model.

[b] BMI and diabetes duration values represent the average in the study population;

[c] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

The Committee concluded the following:

Low carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on fasting plasma glucose within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

There is no MA that addresses the effect of advising low carbohydrate diets separately from moderate carbohydrate diets. There are two individual RCTs that address advising low carbohydrate diets. This is too few to base conclusions on.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to substitution effects:

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising moderate carbohydrate diets compared with advising diets high in carbohydrates on fasting plasma glucose within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There is no MA that addresses the effect of advising moderate carbohydrate diets separately from low carbohydrate diets. There are 3 individual RCTs that address advising moderate carbohydrate diets, with more than 90 participants, which excludes a conclusion with strong evidence.
2. Substantial heterogeneity in the direction of the effects is present, with one RCT showing a reducing effect, one RCT an increasing effect, and one RCT no effect. The RCT with an increasing effect had an imbalance in baseline glucose values. Baseline glucose values of the control group were higher than in the intervention group. Due to this, there may have been more room for improvement of glucose values in the control group. Furthermore, all three studies had a high risk of bias (among others, due to incomplete outcome data), and this may have caused heterogeneity. Due to this, the Committee concluded that the overall quality of the evidence is too low to base conclusions on.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that, where reported, compliance with the moderate carbohydrate diets was good overall and therefore is unlikely to have contributed to the heterogeneity in effects.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

No MAs that addressed the effect of advising low carbohydrate diets were available. Therefore, the Committee evaluated two single RCTs. One RCT, of Shai et al.[50], was abstracted from a MA of van Zuuren et al.[10] (which combined low and moderate carbohydrate diet studies; see Table 17a).

That study lasted for 12 months. Furthermore, a recently published RCT, of Tay et al.[15], contributed to the evaluation of the evidence. The RCT lasted 24 months. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. The RCT of Tay et al. was isocaloric whereas the RCTs of Shai et al. was not. Comparator diets were defined as high carbohydrate and/or low fat diets.

Shai et al. found a statistically significant reduction in fasting plasma glucose whereas Tay et al. did not find an effect of advising low carbohydrate diets compared with advising high carbohydrate diets.

These two RCTs provide too little evidence for the Committee to base conclusions on. Therefore, the Committee did not further evaluate the quality of the evidence of those studies.

Moderate carbohydrate diets

No MAs that addressed the effect of advising moderate carbohydrate diets were available. Therefore, the Committee abstracted three RCTs from a MA of van Zuuren et al.[10] (that combined low and moderate carbohydrate diet studies; see Table 17a), of Elhayany et al.[46], Hockaday et al.[54] and Wolever et al.[26] The 3 RCTs were rather similar in size, with 93 to 116 participants in each RCT, and all had study durations of 12 months. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. The recommendations given in the RCTs of Elhayany et al. and Hockaday et al. were isocaloric, whereas the recommendations of Wolever et al. were not. Comparator diets were defined as high carbohydrate and/or modified fat diets. One RCT (Elhayany et al.) defined the comparator diet as according to standard diabetes recommendations.

There was substantial heterogeneity in effects between studies, with Elhayany et al. reporting a reducing effect on fasting plasma glucose, Hockaday et al. an increasing effect, and Wolever et al. no effect. Particularly the RCT of Hockaday et al. caused heterogeneity. Van Zuuren et al. reported that an imbalance in baseline glucose levels between groups may have caused the heterogeneity. In addition, the low glycaemic index foods consumed by the control group of the study of Wolever et al. may have caused the heterogeneity.

Substitution by protein or fat

All 3 RCTs advised substitution of the carbohydrates in the moderate carbohydrate diet by fat, of which two particularly by MUFAs and one particularly by SFA. In the RCT of Hockaday et al.[54], SFA was used for the substitution. This is unlikely to have contributed to a large extent to the increasing effect on glucose.

Retention rates

Retention rates ranged from 72 to 100% in the moderate carbohydrate diets groups, and from 65 to 100% in the high carbohydrate diet groups, with the lowest reported by Elhayany et al.[46] (further discussed below).

Risk of bias

The RCT of Elhayany et al.[46] was scored as high risk of bias due to (among others) a high total number of dropouts. Although the dropouts were balanced between the groups, van Zuuren et al.[10] judged it high risk of bias since the analyses were performed according to per protocol analysis.

Even though van Zuuren et al. did not score the RCTs of Wolever et al.[26] and Hockaday et al.[54] as high risk of bias, those RCTs are worth noting with respect to bias. In the study of Hockaday et al., baseline glucose values of the control group were higher than in the intervention group. Due to this, there may have been more room for improvement of glucose values in the control group. The study of Wolever et al. was scored as high risk of bias by other MA authors (see Annex K) since data was reported for completers only, and there was a 20% drop out in each group. Also, the first author is president and part-owner of GI Index Testing Inc.

Van Zuuren et al. reported the overall quality for combined low and moderate carbohydrate diets of the evidence regarding fasting plasma glucose of >26 weeks. It was graded as moderate, particularly due to inconsistency in the findings.

Publication bias

Van Zuuren et al.[10] did not assess publication bias because there were too few studies that evaluated the effect on fasting plasma glucose at the same specific time points.

Dietary compliance

Hockaday et al.[54] did not report achieved dietary intakes. For the other two RCTs, achieved carbohydrate intakes in the moderate carbohydrate diet groups were within the range of moderate carbohydrate diets. The contrast in achieved carbohydrate intakes between intervention and control group was small in the RCT of Elhayany et al.[46] (3 en%). This RCT found a reducing effect on fasting plasma glucose, which is unlikely to be due to a small contrast in intake.

Summary

There was a high level of heterogeneity between three RCTs that addressed the effects of advising moderate compared with high carbohydrate diets on fasting plasma glucose in the longer term. All three studies had a high risk of bias (due to imbalances in baseline values of glucose or due to incomplete outcome data), and this may have caused heterogeneity. The long-term compliance with moderate carbohydrate

diets was good although the contrast in intake with the control group was small in one of the RCTs.

3.5 LDL cholesterol

3.5.1 Short-term effects on LDL cholesterol

Tables 19 and 19a summarise the results and characteristics of the MAs, and RCTs included in one of the MA, that provided evidence regarding the effects of advising low and moderate carbohydrate diets on LDL cholesterol in the short term. In addition, Table 20 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MAs are provided in **Annex G**.

Table 19 Short-term effects of advising low and moderate carbohydrate diets on LDL cholesterol in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Korsmo-Haugen, 2018[18]; 3 to 6 months	Van Zuuren, 2018[10]; 4 to 6 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤40 en%; c: >40 en%	i: ≤40 en%; c: >40 en%
Number of studies; total number of participants	6 RCTs; 345	5 RCTs; 372
Number of studies according to category of carbohydrate restriction	Very low: 1 Low: 2 Moderate: 3	Very low: 1 Low: 4 Moderate: 0
Heterogeneity	High: 50%	N0: 0%
Strength of the effect: WMD[a] (95%CI)	Effect estimates per RCT included in the MA are shown in Table 19a[b]	0.02 (-0.09, 0.13) mmol/L
Study population	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]:oral agents, insulin, and none (diet only) in one RCT[d]; Europe, USA, Canada, Japan, Australia	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin; Europe, USA, Japan, Australia

CI: confidence interval; LDL: low-density lipoprotein; MA: meta-analysis; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean difference in LDL cholesterol change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] No pooled effect estimate is presented in the current background document since the studies included in the MA were heterogeneous and combined low and moderate carbohydrate diets. Therefore, the Committee evaluated the evidence on RCT level, to allow separate conclusions on effects of advising low and moderate carbohydrate diets;

[c] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications);

[d] The RCT of McLaughlin et al.55 included participants that did not use any diabetes medications (oral agents or insulin).

Table 19a Short-term effects of low and moderate carbohydrate diets on LDL cholesterol in RCTs included in the meta-analysis of Korsmo-Haugen et al.[18]

RCT	Number of participants	Category of carbohydrate restriction	Effect (95%CI), mmol/L
Jonasson, 2014[29]	59	Low carbohydrate diet	0.20 (-0.21, 0.61)
Westman, 2008[31]	50	Low carbohydrate diet	-0.10 (-0.59, 0.39)
Yamada, 2014[52]	24	Low carbohydrate diet	-0.40 (-0.84, 0.04)
Jenkins, 2014[56]	141	Moderate carbohydrate diet	-0.24 (-0.33, -0.15)
Luger, 2013[36]	42	Moderate carbohydrate diet	0.26 (-0.21, 0.73)
McLaughlin, 2007[55]	29	Moderate carbohydrate diet	0.13 (-0.52, 0.78)

CI: confidence interval; LDL: low-density lipoprotein; RCT: randomised controlled trial.

Table 20 Short-term effects of advising moderate carbohydrate diets on LDL cholesterol in people with type 2 diabetes: individual RCT.

RCT; Study duration	Liu, 2018[12]; 3 months
Category of carbohydrate restriction	Moderate carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 42 en%; c: 54 en%
Number of participants in intervention (i) and control (c) group	i: 30; c: 30
Strength of the effect: Mean difference (95%CI)	No statistically significant difference between groups. Effect estimate NR.
Study population	People newly diagnosed with type 2 diabetes; men and women; BMI[a]: 24 kg/m^2 (i) and 25 kg/m^2 (c); diabetes medications: none (diet only); China (Asia)

BMI: body mass index; CI: confidence interval; LDL: low-density lipoprotein; NR: not reported.

[a] BMI values represent the average in the study population.

The Committee concluded the following:

Low carbohydrate diets

Intervention studies show there is likely no difference in the effect of advising low carbohydrate diets compared with advising diets high in carbohydrates on LDL cholesterol within 3 to 6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 7 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is no obvious heterogeneity in directions of effects in the RCTs.
3. There is no statistically significant effect in the MA.
4. The Committee noted some studies had moderate retention rates, and two of the included RCTs were at high risk of bias (among others, due to the risk of incomplete outcome data). However, the Committee expects this is unlikely to have impacted the conclusions, given the lack of heterogeneity between studies. Based on this, the Committee drew the conclusion there is likely no difference in effect, and there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that, where reported, very low carbohydrate diet studies had low dietary compliance, and for low carbohydrate diet studies the compliance was variable. This may (partly) explain the lack of effect found in the MA. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the low compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein. Nevertheless, the Committee notes that, based on what is known from studies in the general population, it is expected that particularly the subgroups of fat used in the substitution of carbohydrates will impact LDL cholesterol levels. As is stated in the background document *Verzadigde, enkelvoudig en meervoudig onverzadigde (n-6) vetzuren* of the *Dutch dietary guidelines 2015*[57], there is strong evidence from RCTs that substitution of carbohydrates with saturated fat increases LDL cholesterol, whereas substitution of carbohydrates with cis-MUFAs or cis-PUFAs lowers LDL cholesterol.

Moderate carbohydrate diets

There is contradictory evidence regarding the effect of advising moderate carbohydrate diets compared with advising diets high in carbohydrates on LDL cholesterol within 3-6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There is no MA that addresses the effect of advising moderate carbohydrate diets separately from low carbohydrate diets. There are 4 individual RCTs, with more than 90 participants, which excludes a conclusion with strong evidence.
2. There is heterogeneity in effects between RCTs that addressed moderate carbohydrate diets, with the largest RCT showing a reduced effect, and three RCTs showing no effect. The Committee notes that contradictory results are as expected since this is likely (to a great extent) due to differences in the dietary fat (subgroups) compositions of the different studies (as is also explained in the section *Regarding substitution effects* below. More specifically, the largest RCT (that particularly caused the heterogeneity) prescribed alpha-linoleic acid

(and MUFA) as a substitute for carbohydrates. This may explain the reducing effect found on LDL cholesterol. The other RCTs prescribed protein (2 RCTs) or unknown types of (particularly unsaturated) fat (1 RCT) as substitutes for carbohydrates. There may also be other reasons for heterogeneity, such as other characteristics of the study diets or participant characteristics.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that compliance with the moderate carbohydrate diets was good overall and therefore unlikely to have contributed to the heterogeneity in effects. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the good compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein. Nevertheless, the Committee notes that, based on what is known from studies in the general population, it is expected that particularly the subgroups of fat used in the substitution of carbohydrates will impact LDL cholesterol levels. As is stated in the background document *Verzadigde, enkelvoudig en meervoudig onverzadigde (n-6) vetzuren* of the *Dutch dietary guidelines 2015*[57], there is strong evidence from RCTs that substitution of carbohydrates with saturated fat increases LDL cholesterol, whereas substitution of carbohydrates with cis-MUFAs or cis-PUFAs lowers LDL cholesterol.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

The MA of van Zuuren et al.[10] was included in the evaluation since only (very) low carbohydrate diet studies were included in the MA of LDL cholesterol. The MA included 5 RCTs of which 1 was a very low and 4 were a low carbohydrate diet intervention, with a total of 372 participants. The RCT of Davis et al.[28] had the largest weight in the MA. Two of the included RCTs were isocaloric. Comparator diets were defined as low calorie and/or low fat and/or high carbohydrate.

In addition, two RCTs included in the MA of Korsmo-Haugen et al.[18] were included in the evaluation, of Jonasson et al.[29], and Westman et al.[31] (a third RCT that met the inclusion criteria, of Yamada et al.[52], was already

included in the MA of van Zuuren et al.). The RCT of Westman et al. evaluated very low carbohydrate diets, was not isocaloric and defined the comparator diet as low glycaemic index, reduced calories. The RCT of Jonasson et al. evaluated low carbohydrate diets, was isocaloric and defined the comparator diet as low fat.

In the RCTs, participants were generally recommended to reduce body weight and/or energy intake.

The MA of van Zuuren et al. reported no effect of advising low carbohydrate diets on LDL cholesterol (WMD 0.02 (-0.09, 0.13) mmol/L) compared with advising high carbohydrate diets, without heterogeneity between studies. In addition, the two low carbohydrate diet RCTs abstracted from the MA of Korsmo-Haugen et al. both found no effect of advising low carbohydrate, in line with the MA result of van Zuuren et al.

Subgroup or sensitivity analyses

No relevant subgroup analyses were performed by van Zuuren et al.[10]

Substitution by protein or fat

Where the substitution was specified, all RCTs advised substituting the carbohydrates in the low carbohydrate diet with a combination of fat and protein. Therefore, no meaningful subgroup analyses by substitution of protein or fat was possible. Where specified, the fat substitution was with MUFAs or a combination of MUFAs with either SFAs or PUFAs.

Retention rates

Retention rates ranged from 55 to 100% in the low carbohydrate diet groups and from 63 to 100% in the high carbohydrate diet groups. Particularly, the RCT of Westman et al.[31] had low retention rates (55 and 63%, in low and high carbohydrate diet groups, respectively).

Risk of bias

In the MA of van Zuuren et al.[10], no RCTs were scored as high risk of bias. The two RCTs abstracted from the MA of Korsmo-Haugen et al.[18] (Westman et al.[31] and Jonasson et al.[29]) were both scored as high risk of bias, both particularly because of high risk of bias due to lack of blinding and because of unclarities regarding the completeness of data. However, since there was no heterogeneity between studies, it is not expected to have impacted the overall result.

Van Zuuren et al. reported the overall quality for combined low and moderate carbohydrate diets of the evidence regarding LDL cholesterol at 16-26 weeks. It was graded as high quality of evidence. Korsmo-Haugen et al. reported the overall quality of the evidence for combined low and moderate carbohydrate diets and combined short and long-term studies. It was graded as low quality of evidence since the majority of studies were

scored as high or unclear risk of bias, and because of inconsistency in the study findings.

Publication bias

Van Zuuren et al.[10] did not assess publication bias because there were too few studies that evaluated the effect on LDL cholesterol at the same specific time points. Korsmo-Haugen et al.[18] did assess publication bias for combined low and moderate carbohydrate diets and combined short and long-term studies, and reported there was no evidence for publication bias.

Dietary compliance

Where reported, the achieved intakes of carbohydrates in the (very) low carbohydrate diet intervention group were generally in line with the prescribed intakes, with the exception of the RCT of Davis et al.[28]
In this RCT, achieved intakes in the low carbohydrate diet group were comparable to moderate carbohydrate diets. This may have contributed to the lack of effect in that particular study.

Summary

The MA of van Zuuren et al.[10] and two RCTs abstracted from the MA of Korsmo-Haugen et al.[18] reported no differences in the effect of advising low carbohydrate diets compared with advising high carbohydrate diets on LDL cholesterol, without heterogeneity between studies. Some RCTs had moderate numbers of losses to follow-up, and two were scored as high risk of bias, among others because of unclarities regarding the completeness of outcome data. However, since no heterogeneity between studies was detected, it is not expected to have impacted the overall conclusion of no effect. Compliance with the (very) low carbohydrate diet was generally good.

Moderate carbohydrate diets

Study characteristics and main effects

There was no MA that specifically addressed the effects of advising moderate carbohydrate diets. Therefore, three RCTs, that addressed effects of advising moderate carbohydrate diets, abstracted from the MA of Korsmo-Haugen et al.[18], were included in the current evaluation.
The RCT of Jenkins et al.[56] had the largest number of participants included. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Of the 3 moderate carbohydrate diet studies included in the MA, two were isocaloric. The comparator diets were defined as low glycaemic load, high fat, high carbohydrate or according to standard dietary guidelines for diabetes.

Two of the RCTs (Luger et al.[36] and McLaughlin et al.[55]) included by Korsmo-Haugen et al., and the recent RCT of Liu et al.[12], found no differences in the effect of advising moderate carbohydrate diets compared with high carbohydrate diets on LDL cholesterol. It should be

noted that the effect estimate of 0.26 mmol/L for the study of Luger et al., presented Table 19a, represents the between-group difference in LDL cholesterol at the end of follow-up. However, the between-group difference in the *change* in LDL cholesterol during follow-up is 0.02 mmol/L, which is much smaller, and therefore judged as no difference in effect by the Committee. Contrarily, Jenkins et al. (included by Korsmo-Haugen et al.) found a reducing effect on LDL cholesterol. In the study of Jenkins et al., the moderate carbohydrate diet group received alpha-linoleic acid (and MUFA) in the form of canola-enriched bread supplements. This may explain the reducing effect found by Jenkins et al. There may also be other reasons for heterogeneity, such as other characteristics of the study diets or participant characteristics.

Substitution by protein or fat

Two RCTs advised substituting the carbohydrates in the moderate carbohydrate diet with fat, particularly (M)UFAs. The other two RCTs advised substituting the carbohydrates with protein. The types of protein are unknown. Due to the limited numbers of RCTs per type of substitution, no meaningful subgroup analyses by substitution of protein or fat were possible.

Retention rates

Retention rates ranged from 79 to 100% in the moderate carbohydrate diet groups, and from 83 to 100% in the high carbohydrate diet groups. The lowest retention rate was found in the RCT of Jenkins et al.[56] (further explained below).

Risk of bias

One of the RCTs, of Luger et al.[36], was scored as high risk of bias. This was particularly due to unclarities regarding the randomisation and allocation procedures and lack of blinding. Although this may have contributed to the heterogeneity between studies, it is not expected to have had a major impact on the overall findings since the RCT was relatively small in terms of participants included.

The moderate retention rates reported by Jenkins et al.[56] are not likely to have affected the RCT result since the reasons for dropout were not related to the intervention for the majority of participants, and the reasons for dropout were not different from those in the high carbohydrate diet group.

Korsmo-Haugen et al.[18] reported the overall quality of the evidence for combined low and moderate carbohydrate diets and combined short and long-term studies. It was graded as low quality of evidence since the majority of studies were scored as high or unclear risk of bias, and because of inconsistency in the study findings.

Publication bias

Korsmo-Haugen et al.[18] did assess publication bias for combined low and moderate carbohydrate diets and combined short and long-term studies, and reported there was no evidence for publication bias.

Compliance

Where reported, the achieved intakes in the moderate carbohydrate diet groups were comparable to the prescribed intakes.

Summary

Three RCTs did not find differences in the effects of advising moderate compared with high carbohydrate diets on LDL cholesterol. In contrast, a fourth, large-scale RCT found a reducing effect on LDL cholesterol, making the evidence heterogeneous. Differences in dietary fat (subgroup) composition of the study diets may have caused the heterogeneity. One of the RCTs was judged at high risk of bias. However, the impact on the overall conclusion is expected to be minor due to the small sample size of this study. The compliance with the moderate carbohydrate diets was good overall.

3.5.2 Longer-term effects on LDL cholesterol

Table 21 summarises the results and characteristics of the MAs that provided evidence regarding the effects of advising low and moderate carbohydrate diets on LDL cholesterol in the longer term. In addition, Table 22 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MAs are provided in **Annex H**.

Table 21 Long-term effects of advising low and moderate carbohydrate diets on LDL cholesterol in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Korsmo-Haugen, 2018[18]; ≥12 months	Huntriss, 2018[9]; ≥12 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤40 en%; c: >40 en%	No cut-offs. Carbohydrate intake should be lower in i than c.
Number of studies; total number of participants	9 RCTs; 1064	5 RCTs; 389
Number of studies according to category of carbohydrate restriction	Very low: 0 Low: 2 Moderate: 7	Very low: 1 Low: 3 Moderate: 1
Heterogeneity	Yes: 51%	No: 0%
Strength of the effect: WMD[a] (95%CI)	Effect estimates per RCT included in the MA are shown in Table 23[b]	0.05 (-0.10, 0.19) mmol/L
Study population	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin, and none (diet only) in one RCT[d]; Europe, USA, Canada, Australia, New Zeeland, Israel	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin; Europe, USA, Australia

CI: confidence interval; LDL: low-density lipoprotein; MA: meta-analysis; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean difference in LDL cholesterol change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] No pooled effect estimate is presented in the current background document since the studies included in the MA were heterogeneous and combined low and moderate carbohydrate diets. Therefore, the Committee evaluated the evidence on RCT level, to allow separate conclusions on effects of advising low and moderate carbohydrate diets. The effect estimates per RCT included in the MA are shown in Table 23, for moderate carbohydrate diet studies. The low carbohydrate diet studies were covered in the MA of Huntriss et al.[9];

[c] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

[d] The RCT of Wolever et al.[26] included participants that did not use any diabetes medications (oral agents or insulin).

Table 22 Long-term effects of advising low carbohydrate diets on LDL cholesterol in people with type 2 diabetes: individual RCTs.

RCT; Study duration	Saslow, 2017[14]; 12 months	Sato, 2017[16]; 18 months	Tay, 2018[15]; 24 months
Category of carbohydrate restriction	Very low carbohydrate diet	Low carbohydrate diet	Low carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 20 to 50 g; c: 45 to 50 en%	i: 130 g; c: 50 to 60 en%	i: 14 en%; c: 53 en%
Number of participants in intervention (i) and control (c) group	i: 16; c: 18	i: 33; c: 33	i: 58; c: 57
Strength of the effect: Mean difference (95%CI)[a]	-0.5 mg/dL [-0.01 mmol/L]; 95%CI: NR; p-value <0.20[b]	-5 mg/dL [-0.13 mmol/L]; 95%CI: NR; p-value 0.57[c]	0.1 (-0.3, 0.5) mmol/L[b]
Study population	People diagnosed with type 2 diabetes or pre-diabetes; diabetes duration[d]: 7 years; men and women; BMI[d]: 37 kg/m^2; diabetes medications[e]: oral agents; USA	People diagnosed with type 2 diabetes; diabetes duration[d]: 13 (i) and 14 (c) years; men and women; BMI[d]: 27 kg/m^2; diabetes medications[e]: oral agents, insulin; Japan	People diagnosed with type 2 diabetes; diabetes duration[d]: 7 years; men and women; BMI[d]: 35 kg/m^2; diabetes medications[e]: oral agents insulin; Australia

BMI: body mass index; CI: confidence interval; LDL: low-density lipoprotein; NR: not reported; RCT: randomised controlled trial; USA: United States of America.

[a] Values are the differences in estimated marginal mean changes between low and high carbohydrate diet groups;

[b] p-value was derived from mixed effects linear regression model;

[c] p-value was derived from Mann-Whitney U test.

[d] BMI and diabetes duration values represent the average in the study population; [e]Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

The Committee concluded the following:

Low carbohydrate diets

Intervention studies show there is likely no difference in the effect of advising low carbohydrate diets compared with advising diets high in carbohydrates on LDL cholesterol within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 7 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong or to allow a conclusion of no effect.
2. There is no obvious heterogeneity in direction of effects between studies.
3. There is no statistically significant effect in the MA.
4. The Committee noted that some studies had moderate retention rates. However, the Committee expects this is unlikely to have impacted the conclusions since there was no heterogeneity between studies. Based on this, the Committee concluded there are no other relevant considerations.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that very low carbohydrate diet studies had low dietary compliance, and for low carbohydrate diet studies the compliance was variable. This may have attenuated the effect sizes of the evaluated RCTs. Given that the Committee evaluated the effect of *advising* diets low in carbohydrates rather than *consuming* diets low in carbohydrates, the lower compliance can be seen as part of the effect under evaluation, and does not impact the quality of the evidence.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein. Nevertheless, the Committee notes that, based on what is known from studies in the general population, it is expected that particularly the subgroups of fat used in the substitution of carbohydrates will impact LDL cholesterol levels. As is stated in the background document *Verzadigde, enkelvoudig en meervoudig onverzadigde (n-6) vetzuren* of the *Dutch dietary guidelines 2015*[57], there is strong evidence from RCTs that substitution of carbohydrates with saturated fat increases LDL cholesterol, whereas

substitution of carbohydrates with cis-MUFAs or cis-PUFAs lowers LDL cholesterol.

Moderate carbohydrate diets

Intervention studies show there is contradictory evidence regarding the effect of advising moderate carbohydrate diets compared with advising diets high in carbohydrates on LDL cholesterol within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There is no MA that addresses the effect of advising moderate carbohydrate diets separately from low carbohydrate diets. There are 7 individual RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as contradictory, as explained below.
2. There is heterogeneity in directions of effects between studies with one RCT showing an (almost) statistically significant reducing effect, another showing a statistically significant increasing effect on LDL cholesterol, and the remaining 5 RCTs showing no effect. It may be partly explained by high risk of bias in two of the RCTs, but this is unlikely to fully explain the heterogeneity. Also, the Committee notes that contradictory results can be expected when there are differences in the dietary fat (subgroups) compositions of the different study diets. This is further explained in the section *Regarding substitution effects* below. In the current evaluation, differences in fat substitutions are unlikely to fully explain the heterogeneity since only a few studies substituted the carbohydrates with fat. Heterogeneity may also be explained by factors such as differences in other characteristics of the study diets or changes in use of LDL-lowering medication. Based on the high level of heterogeneity, the Committee concluded that the evidence is contradictory.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to dietary compliance and substitution effects:

Regarding compliance: The Committee noted that compliance with the moderate carbohydrate diets was good overall and is therefore unlikely to have contributed to the heterogeneity in effects.

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein. Nevertheless, the Committee notes that, based on what is known from studies in the general

population, it is expected that particularly the subgroups of fat used in the substitution of carbohydrates will impact LDL cholesterol levels. As is stated in the background document *Verzadigde, enkelvoudig en meervoudig onverzadigde (n-6) vetzuren* of the *Dutch dietary guidelines 2015*[57], there is strong evidence from RCTs that substitution of carbohydrates with saturated fat increases LDL cholesterol, whereas substitution of carbohydrates with cis-MUFAs or cis-PUFAs lowers LDL cholesterol.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

One MA, of Huntriss et al.[9] was included in the evaluation of the effects of advising low carbohydrate diets on LDL cholesterol. The MA included 1 very low, 3 low and 1 moderate carbohydrate diet interventions. Since there was no heterogeneity between studies included in the MA and the vast majority addressed (very) low carbohydrate diets, the Committee judged the evidence applicable to low carbohydrate diets.

Study durations of the included RCTs were 12 months (with the exception of one RCT with an 11-month duration). Of the low carbohydrate diet RCTs, the study of Davis et al.[28] had the largest weight in the MA. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Two of the low carbohydrate diet RCTs included in the MA were isocaloric, and two were not. Comparator diets were defined as calorie restricted and/or low fat and/or high carbohydrate.

The MA of Huntriss et al. showed no statistically significant effect on LDL cholesterol when advising low or moderate carbohydrate diets compared with high carbohydrate diets, without heterogeneity between studies (WMD 0.05 (-0.10, 0.19) mmol/L).

In addition, three recent RCTs were included in the evaluation[14-16]. Those RCTs addressed (very) low carbohydrate diet interventions with durations of 12 to 24 months. One was isocaloric, the other two were not. The comparator diets were defined as high or moderate carbohydrate, calorie restricted, and/or low fat. One of the RCTs, of Tay et al.[15], was also included in the MA of Huntriss et al., but with a shorter duration (12 versus 24 months). All recent RCTs found no difference in effect on LDL cholesterol, in line with the MA finding.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed by Huntriss et al.[9]

Substitution by protein or fat

For all low carbohydrate diet RCTs, the carbohydrates were advised to be substituted by a combination of both protein and fat (MUFA or combined MUFA with SFA or PUFA) or it was unclear regarding this aspect.

Therefore, it was not possible to perform subgroup analyses by substitution of protein or fat.

Retention rates

Retention rates ranged from 57 to 87% in the low carbohydrate diet groups, and from 49 to 90% in the high carbohydrate diet groups. Particularly in the RCTs of Tay et al.[15], retention was low (further discussed below).

Risk of bias

In the MA of Huntriss et al.[9], no study-specific risk of bias assessments was presented. Huntriss et al. reported that the risk of bias was high in the majority of included studies due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention. Particularly the RCT of Tay et al.[15] had high numbers of dropouts. Given the lack of heterogeneity between the RCTs included in the MA, it is not expected that the studies at high risk of bias impacted the overall conclusion.

Of the three individual, recent, RCTs, none were scored as high risk of bias. The RCT of Sato et al.[16] had *some concerns* regarding risk of bias since the dropout was higher in the control group. Given the lack of heterogeneity between studies, it is not expected that studies with high risk of bias affected the overall result.

Publication bias

Huntriss et al.[9] did not assess presence of publication bias.

Compliance

The studies of Mayer et al.[58] (included in the MA) and Saslow et al.[14] (individual recent RCT), that addressed very low carbohydrate diets, had achieved intakes in line with low carbohydrate diets instead of very low carbohydrate diets. This may have contributed (to some extent) to the lack of effects on LDL cholesterol.

The low carbohydrate diet studies had achieved intakes that were within the range of low carbohydrate diets, with the exception of the individual RCTs of Davis et al.[28], and of Sato et al.[16] In those RCTs, carbohydrate intakes in the low carbohydrate diet group were in line with moderate carbohydrate diets. Furthermore, in the RCT of Sato et al., intakes of carbohydrates were comparable between the intervention and control group, leaving no contrast between intervention and control. This may have contributed to the lack of effect on LDL cholesterol.

Summary

The MA of Huntriss et al.[9] showed no effect of advising low carbohydrate diets on LDL cholesterol in the longer term, without heterogeneity between studies. This was confirmed by recent RCTs. Some studies had moderate retention rates. Due to the lack of heterogeneity between studies it is not

expected that this impacted the conclusions. Risk of bias was not presented on RCT level for the MA of Huntriss et al. For the recent RCTs, none were scored at high risk of bias. Compliance was variable for low carbohydrate diets. For very low carbohydrate diets, achieved intakes were in line with low carbohydrate diets, suggesting that it is difficult to comply with a very low carbohydrate diet in the long term. This may have contributed to the lack of effects.

Moderate carbohydrate diets

Study characteristics and main effects

No MAs that addressed the effects of advising moderate carbohydrate diets separately from low carbohydrate diets on LDL cholesterol were available. Therefore, the Committee evaluated 7 RCTs included in the MA of Korsmo-Haugen et al.[18] The MA of Korsmo-Haugen et al. initially included 2 low, and 7 moderate carbohydrate diet studies. Study durations varied from 12 to 47 months. The RCT of Wolever et al.[26] was the largest in terms of numbers of participants included. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Out of the 7 moderate carbohydrate diet interventions, 5 were isocaloric. Comparator diets were defined as high carbohydrate and/or low fat, low protein or according to standard treatment guidelines.

Although most RCTs did not find statistically significant effects of advising moderate compared with high carbohydrate diets, there was substantial heterogeneity between studies, with some showing (almost) statistically significant reducing and other showing (almost) statistically significant increasing effects on LDL cholesterol. Heterogeneity may be explained by factors such as differences in characteristics of the study diets or changes in use of LDL-lowering medication. However, the heterogeneity was not explained by Korsmo-Haugen et al.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed by Korsmo-Haugen et al.[18]

Substitution by protein or fat

In total, four RCTs advised substituting the carbohydrates of the moderate carbohydrate diet with protein, two with fat, specifically MUFA, and one with a combination of protein and fat (particularly MUFA). The types of protein were not specified. Results are shown in Table 23. Given that only two studies advised fat substitutions, a comparison of effects between protein and fat substitutions was not feasible.

Table 23 Long-term effects of moderate carbohydrate diets compared with high carbohydrate diets on LDL cholesterol (mmol/L): RCTs with substitutions for protein and fat.

RCT	Number of participants	Substitution(s)	Mean difference (95%CI) in LDL cholesterol (mmol/L)
Elhayany, 2010[46]	179	Fat	-0.19 (-0.42, 0.04)
Wolever, 2008[26]	156	Fat	-0.07 (-0.20, 0.06)
Brinkworth, 2004[47]	38	Protein	-0.50 (-1.13, 0.13)
Krebs, 2012[34]	294	Protein	0.10 (-0.11, 0.31)
Larsen, 2011[35]	99	Protein	-0.10 (-0.37, 0.17)
Pederson, 2014[48]	45	Protein	0.30 (0.02, 0.58)
Facchini, 2003[59]	101	Fat & protein	0.21 (-0.42, 0.84)

CI: confidence interval; LDL: low-density lipoprotein; RCT: randomised controlled trial.

Retention rates

Retention rates ranged from 56 to 91% in the moderate carbohydrate diet groups and from 61 to 87% in the high carbohydrate diet groups.

Risk of bias

Korsmo-Haugen et al.[18] scored two RCTs, of Facchini et al.[59] and Elhayany et al.[46], as high risk of bias, both due to unclarities regarding the procedures of randomisation and allocation concealment and blinding of outcome assessors. For Elhayany et al., a high risk of selective reporting was also detected. Both studies may have contributed to the heterogeneity in results. However, based on results presented in the forest plot of the MA, the Committee expects heterogeneity to remain present even after discarding those two studies.

Korsmo-Haugen et al. reported the overall quality of the evidence for combined low and moderate carbohydrate diets and combined short and long-term studies. It was graded as low quality of evidence since the majority of studies were scored as high or unclear risk of bias, and because of inconsistency in the study findings.

Publication bias

Korsmo-Haugen et al.[18] assessed publication bias for combined low and moderate carbohydrate diets and combined short and long-term studies, and reported there was no evidence for publication bias.

Dietary compliance

The RCTs that addressed the effects of advising moderate carbohydrate diets had good compliance with the moderate carbohydrate diets, based on reported achieved intakes. In some RCTs (e.g. Elhayany et al.[59], Krebs et al.[34], Larsen et al.[35]), contrasts in achieved carbohydrate intakes between intervention and control groups were rather small (4 en% or less).

Summary

RCTs that addressed effects of advising moderate compared with high carbohydrate diets found heterogeneous effects on LDL cholesterol. The heterogeneity may be partly explained by RCTs at high risk of bias, but other factors such as differences in characteristics of the study diets or

changes in use of LDL-lowering medication may also have contributed to heterogeneity. Adherence to the moderate carbohydrate diet was good, although contrasts in achieved carbohydrate intakes between intervention and control groups were minor in some of the RCTs.

3.6 Systolic blood pressure

3.6.1 Short-term effects on systolic blood pressure

Table 24 summarises the results and characteristics of the MAs that provided evidence regarding the effects of advising low and moderate carbohydrate diets on systolic blood pressure in the short term.

In addition, Table 25 summarises results and characteristics of recently published individual RCTs regarding this topic. Details of RCTs included in the MAs and the individual RCTs are provided in **Annex I**.

Table 24 Short-term effects of advising low and moderate carbohydrate diets on systolic blood pressure in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Korsmo-Haugen, 2018[18]; 3 to 6 months	Van Zuuren, 2018[10]; 4 to 6 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤40 en%; c: >40 en%	i: ≤40 en%; c: >40 en%
Number of studies; total number of participants	6 RCTs; 365	4 RCTs; 283
Number of studies according to category of carbohydrate restriction	Very low: 1 Low: 2 Moderate: 3	Very low: 0 Low: 4 Moderate: 0
Heterogeneity	No: 0%	No: 0%
Strength of the effect: WMD[a] (95%CI)	-0.33 (-2.31, 1.65) mmHg	-0.76 (-3.42, 1.90) mmHg
Study population	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[b]: oral agents, insulin, and none (diet only) in one RCT[c]; Europe, USA, Canada, Australia, Japan	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[b]: oral agents, insulin; Europe, USA, Australia, Japan

CI: confidence interval; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean difference in systolic blood pressure change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications);

[c] The RCT of McLaughlin et al.[55] included participants that did not use any diabetes medications (oral agents or insulin).

Table 25 Short-term effects of advising moderate carbohydrate diets on systolic blood pressure in people with type 2 diabetes: individual RCT.

RCT; Study duration	Liu, 2018[12]; 3 months
Category of carbohydrate restriction	Moderate carbohydrate diet
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 42 en%; c: 54 en%
Number of participants in intervention (i) and control (c) group	i: 30; c: 30
Strength of the effect: Mean difference (95%CI)	No statistically significant difference between groups. Effect estimate NR.
Study population	People newly diagnosed with type 2 diabetes; men and women; average BMI: 24 kg/m^2 (i) and 25 kg/m^2 (c); diabetes medications: none (diet only); China (Asia)

BMI: body mass index; CI: confidence interval; NR: not reported; RCT: randomised controlled trial.

The Committee concluded the following:

Low carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising low carbohydrate diets compared with advising diets high in carbohydrate on systolic blood pressure within 3 to 6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 6 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as too little, as explained below.
2. There is no statistically significant effect in the MA, and there is no obvious heterogeneity in the effects reported in the RCTs.
3. The Committee noted that the individual RCTs and the MA may have insufficient statistical power to demonstrate an effect on systolic blood pressure. Given the broad confidence intervals presented in the individual RCTs and MA, the Committee cannot completely exclude the possibility that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure. Therefore, the Committee judges there is currently too little research to draw a conclusion.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to substitution effects:

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising moderate carbohydrate diets compared with advising diets high in carbohydrate on systolic blood pressure within 3 to 6 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 4 RCTs, with more than 90 participants included in the evaluation, which excludes a conclusion with strong evidence.
2. There is no statistically significant effect in the MA, and there is no obvious heterogeneity in the effects reported in the RCTs.
3. The Committee noted that the individual RCTs and the MA may have insufficient statistical power to demonstrate an effect on systolic blood pressure. Given the broad confidence intervals presented in the individual RCTs and MA, the Committee cannot completely exclude the possibility that advising moderate compared with high carbohydrate diets increases or decreases systolic blood pressure. Therefore, the Committee judges that there is currently too little research to draw a conclusion.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to substitution effects:

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

The MA of van Zuuren et al.[10] was included in the evaluation since only low carbohydrate diet studies were included in the MA of systolic blood pressure (short term). The MA included 4 low carbohydrate diet RCTs, with a total of 283 participants. The RCTs of Guldbrand et al.[45] and Tay et al.[51] had the largest weight in the MA. Two of the RCTs were isocaloric, whereas the other two were not. Comparator diets were defined as high carbohydrate and/or low fat or calorie restricted.

In addition, the MA of Korsmo-Haugen et al.[18] was included in the evaluation. The MA included 1 very low, 2 low and 3 moderate carbohydrate diet interventions. There was no heterogeneity between studies included in the MA, and therefore, the Committee judged the evidence applicable to low carbohydrate diets. The 3 (very low) carbohydrate diet RCTs contributed approximately equal weights to the MA. One of the

RCTs included by Korsmo-Haugen et al. overlapped with the RCTs included by van Zuuren et al. (Yamada et al.[52]). None of the included (very) low carbohydrate diet RCTs were isocaloric. Comparator diets were defined as low glycaemic index and/or calorie restricted or low fat. In the RCTs of both MAs, participants were generally recommended to reduce body weight and/or energy intake.

Both MAs reported no statistically significant effect of advising low (and moderate) carbohydrate diets on systolic blood pressure in the short term, compared with high carbohydrate diets. The MA of Korsmo-Haugen et al. reported a WMD of -0.33 (-2.31, 1.65) mmHg, and the MA of van Zuuren et al. reported a WMD of -0.76 (-3.42, 1.90) mmHg. Based on those confidence intervals, the Committee notes it cannot be completely excluded that advising low compared with high carbohydrate diets increase or decrease systolic blood pressure.

Subgroup or sensitivity analyses

No relevant subgroup analyses were performed in both MAs.

Substitution by protein or fat

All RCTs advised substituting the carbohydrates in the low carbohydrate diet by a combination of fat and protein. Where specified, the fat substitution was (M)UFA, and in one RCT combined with SFA. Therefore, no subgroup analyses by substitution of specifically protein or fat was possible.

Retention rates

Retention rates varied from 55 to 100% in the low carbohydrate diet groups and from 63 to 100% in the high carbohydrate diet groups. The RCT of Westman et al.[31] had particularly low retention rates (further discussed below). Moreover, van Zuuren et al.[10] noted that the RCTs of Tay et al.[51] and Daly et al.[27] had moderate retention rates (78 to 79% in low carbohydrate diet groups and 76 to 82% in high carbohydrate diet groups), yet balanced between groups. Given the lack of heterogeneity between studies, it is not expected that studies with moderate numbers of losses to follow-up have impacted the results of the MAs.

Risk of bias

In the MA of van Zuuren et al.[10], no RCTs were scored as high risk of bias. Two RCTs included by Korsmo-Haugen et al.[18] (Westman et al.[31] and Yamada et al.[52]) were scored as high risk of bias. Westman et al. was scored as high risk of bias, particularly because of lack of blinding and because of unclarities regarding the completeness of data. Yamada et al. was scored as high risk of bias due to lack of blinding of outcome assessors, high risk of selective reporting, and unclarities regarding the procedure of allocation concealment. Subgroup analyses by low versus high risk of bias RCTs were performed for combined short and long-term

RCTs only, and showed no differences in effects on systolic blood pressure between subgroups of low and high risk of bias. Those analyses are of limited use for the current evaluation due to the combined short and long-term data. However, since there was no heterogeneity between studies in the MA of Korsmo-Haugen et al., it is not expected to have impacted the overall result.

Van Zuuren et al. reported the overall quality for combined low and moderate carbohydrate diets of the evidence regarding systolic blood pressure at 16-26 weeks. It was graded as high quality of evidence. Korsmo-Haugen et al. reported the overall quality of the evidence for combined low and moderate carbohydrate diets and combined short and long-term studies. It was graded as moderate quality of evidence since the majority of studies were scored as high or unclear risk of bias.

Publication bias

Van Zuuren et al.[10] did not assess publication bias because there were too few studies that evaluated the effect of systolic blood pressure at the same specific time points. Korsmo-Haugen et al.[18] did assess publication bias for combined low and moderate carbohydrate diets and combined short and long-term studies, and reported that there was no evidence for publication bias.

Dietary compliance

Achieved carbohydrate intakes in the very low carbohydrate diet group were higher than prescribed. In the low carbohydrate diet RCTs included by of Korsmo-Haugen et al.[18] and van Zuuren et al.[10], achieved intakes of carbohydrates in the low carbohydrate diet groups were generally in line with assigned carbohydrates, with the exception of the RCT of Davis et al.[28] (included by van Zuuren et al.). In this RCT, achieved intakes in the low carbohydrate diet group were comparable to moderate carbohydrate diets.

Summary

The MAs of Korsmo-Haugen et al.[18] and van Zuuren et al.[10] showed no differences in short-term effects of advising low compared with high carbohydrate diets on systolic blood pressure, without heterogeneity between studies. However, the reported confidence intervals were rather wide, and based on that, it cannot be completely excluded that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure. Some studies had moderate retention rates, and two were scored as high risk of bias. However, this is not expected to have impacted the results of the MAs due to the lack of heterogeneity between studies. Compliance with the very low carbohydrate diets was low. For the low carbohydrate diet studies, compliance was variable.

Moderate carbohydrate diets

Study characteristics and main effects

The MA of Korsmo-Haugen et al.[18] was included in the evaluation. The MA included 1 very low, 2 low and 3 moderate carbohydrate diet interventions. There was no heterogeneity between studies included in the MA, and therefore, the Committee judged the evidence applicable to moderate carbohydrate diets. The RCT of Jenkins et al.[56] had the largest weight in the MA. Study durations were 3-4 months. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Two of the RCTs were isocaloric. The comparator diets were defined as low glycaemic load, high carbohydrate, or as conventional diabetes diets.

In addition, the individual, recent, RCT of Liu et al.[12] was included in the evaluation. That study had a duration of 3 months, included 60 participants, and evaluated the effect of advising 42 en% of carbohydrates compared with 54 en%. The study diets were isocaloric and the comparator diet was defined as high in carbohydrate and low in protein.

Both the MA and individual RCT reported no statistically significant effect of advising moderate (and low) carbohydrate diets on systolic blood pressure in the short term, compared with high carbohydrate diets. The MA of Korsmo-Haugen et al. reported a WMD of -0.33 (-2.31, 1.65) mmHg, and the RCT of Liu et al. did not provide an effect estimate. Based on the confidence interval reported by Korsmo-Haugen et al., the Committee notes that it cannot be completely excluded that advising moderate compared with high carbohydrate diets increases or decreases systolic blood pressure.

Subgroup or sensitivity analyses

No relevant subgroup analyses were performed in the MA of Korsmo-Haugen et al.[18]

Substitution by protein or fat

Two RCTs advised substituting the carbohydrates in the moderate carbohydrate diet with fat, particularly (M)UFA. The other two RCTs advised substituting with protein. The type of protein was not specified. This is too little evidence to base conclusions on potential differences between substitution by fat or protein.

Retention rates and risk of bias

Retention rates ranged from 79 to 100% in the moderate carbohydrate diet groups and from 83 to 100% in the high carbohydrate diet groups. The RCT of Jenkins et al.[56] had a lower retention rate in the intervention group compared with control. However, given the lack of heterogeneity between studies, this is unlikely to have influenced the MA result.

Risk of bias

None of the RCTs was scored as high risk of bias.

Korsmo-Haugen et al.[18] reported the overall quality of the evidence for combined low and moderate carbohydrate diets and combined short and long-term studies. It was graded as moderate quality of evidence since the majority of studies were scored as high or unclear risk of bias.

Publication bias

Korsmo-Haugen et al.[18] assessed publication bias for combined low and moderate carbohydrate diets and combined short and long-term studies, and reported there was no evidence for publication bias.

Dietary compliance

The recent, individual RCT of Liu et al.[12] did not report achieved intakes. For the moderate carbohydrate intervention studies included by Korsmo-Haugen et al.[18], achieved intakes of carbohydrates were in line with prescribed intakes for the intervention groups.

Summary

The MA of Korsmo-Haugen et al.[18] showed there is no difference in the effect of advising moderate carbohydrate diets compared with high carbohydrate diets on systolic blood pressure. This was confirmed by a recent RCT. However, the reported confidence intervals were rather wide, and based on that, it cannot be completely excluded that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure. Some RCTs had moderate retention rates, but none of the RCTs were scored as high risk of bias. The compliance with the moderate carbohydrate diets was good.

3.6.2 Longer-term effects on systolic blood pressure

Tables 26 and 26a summarise the results and characteristics of the MAs, and RCTs included in one of the MA, that provided evidence regarding the effects of advising low and moderate carbohydrate diets on systolic blood pressure in the longer term. Details of RCTs included in the MA and the individual RCTs are provided in **Annex J**.

Table 26 Long-term effects of advising low and moderate carbohydrate diets on systolic blood pressure in people with type 2 diabetes: meta-analyses of RCTs.

Meta-analysis; Study duration	Korsmo-Haugen, 2018[18]; ≥12 months	Huntriss, 2018[9]; 11 to 48 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤40 en%; c: >40 en%	No cut-offs. Carbohydrate intake should be lower in i than c.
Number of studies; total number of participants	8 RCTs; 814	7 RCTs; 645
Number of studies according to category of carbohydrate restriction	Very low: 1 Low: 2 Moderate: 5	Very low: 2 Low: 3 Moderate: 2
Heterogeneity	No: 3%	Moderate: 43%
Strength of the effect: WMD[a] (95%CI)	-1.39 (-3.20, 0.43) mmHg	Effect estimates per RCT included in the MA are shown in Table 26a[b]
Study population	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin, and none (diet only) in one RCT[d]; Europe, USA, Canada, New Zeeland, Australia, Israel	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[c]: oral agents, insulin and none (diet only) in one RCT[e]; Europe, USA, Australia, Israel

CI: confidence interval; MA: meta-analysis; RCT: randomised controlled trial; USA: United States of America.

[a] WMD = Weighted mean difference in systolic blood pressure change between low or moderate carbohydrate diet groups compared with high carbohydrate diet groups;

[b] No pooled effect estimate is presented in the current background document since the studies included in the MA were heterogeneous and combined low and moderate carbohydrate diets. Therefore, the Committee evaluated the evidence on RCT level, to allow separate conclusions on effects of advising low and moderate carbohydrate diets;

[c] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications);

[d] The RCT of Wolever et al.[26] included participants that did not use any diabetes medications (oral agents or insulin);

[e] The RCT of Esposito et al.[60] included participants that did not use any diabetes medications (oral agents or insulin).

Table 26a Long-term effects of low and moderate carbohydrate diets systolic blood pressure in RCTs included in the meta-analysis of Huntriss et al.[9]

RCT	Number of participants	Category of carbohydrate restriction	Effect (95%CI), mmHg
Davis, 2009[28]	105	Low carbohydrate diet	3.80 (-3.70, 11.30)
Goldstein, 2011[61]	41	Low carbohydrate diet	-9.00 (-26.08, 8.08)
Guldbrand, 2012[45]	61	Low carbohydrate diet	2.00 (-5.23, 9.23)
Mayer, 2014[58]	46	Low carbohydrate diet	-11.00 (-18.60, -3.40)
Tay, 2015[51]	78	Low carbohydrate diet	-1.30 (-6.16, 3.56)
Esposito, 2009[60]	215	Moderate carbohydrate diet	-3.10 (-3.79, -2.23)
Larsen, 2011[35]	99	Moderate carbohydrate diet	-4.27 (-8.80, 0.26)

CI: confidence interval; RCT: randomised controlled trial.

The Committee concluded the following:

Low carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising low carbohydrates diets compared with advising diets high in carbohydrates on systolic blood pressure within 11 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There is no MA that addresses the effect of advising low carbohydrate diets separately from low carbohydrate diets. There are 4 individual RCTs, with more than 90 participants included in the evaluation, which excludes a conclusion with strong evidence.

2. There is no statistically significant effect in the majority of RCTs, and there is no obvious heterogeneity in the effects reported in the RCTs.
3. The Committee noted that the individual RCTs may have insufficient statistical power to demonstrate an effect on systolic blood pressure. Given the wide confidence intervals presented in the individual RCTs, the Committee cannot completely exclude the possibility that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure. Therefore, the Committee judges there is currently too little research to draw a conclusion.

The conclusion of the Committee applies studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to substitution effects:

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Moderate carbohydrate diets

There is too little research to draw conclusions regarding the effects of advising moderate carbohydrates diets compared with advising diets high in carbohydrate on systolic blood pressure within 12 to 24 months, in people diagnosed with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are 5 RCTs, with more than 150 participants included in the evaluation, which is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as *too little research*, as explained below.
2. There is no obvious heterogeneity in directions of effects in the studies included in the MA. One additional RCT showed heterogeneous effects from the studies included in the MA but this may be due to other aspects of the advised diet than the carbohydrate content. Therefore, this study was discarded in judging the level of heterogeneity.
3. There is no statistically significant effect in the MA.
4. The Committee noted that the individual RCTs may have insufficient statistical power to demonstrate an effect on systolic blood pressure. Given the wide confidence intervals presented in the individual RCTs, the Committee cannot completely exclude the possibility that low compared with high carbohydrate diets increase or decrease systolic

blood pressure. Therefore, the Committee judges there is currently too little research to draw a conclusion.

The conclusion of the Committee applies to studies in which participants were recommended to reduce body weight and/or energy intake.

Furthermore, the Committee concluded the following with respect to substitution effects:

Regarding substitution effects: There is too little research available to speculate on potential differences in effects when the carbohydrates are advised to be substituted by either fat or protein.

Explanation:

Low carbohydrate diets

Study characteristics and main effects

No MA that addressed the effect of advising low carbohydrate diets were available. Therefore, 5 RCTs contributing to the MA of Huntriss et al.[9] were evaluated. The 3 (very) low carbohydrate diet RCTs included in the MA of Korsmo-Haugen et al.[18] had already been covered in the MA of Huntriss et al., and therefore only the MA of Huntriss et al. was used by the Committee.

Study durations of the RCTs were 11 to 24 months. Of the 5 RCTs, two were very low and three were low carbohydrate diet studies. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Two low carbohydrate diet studies (Guldbrand et al.[45], and Tay et al.[51]) were isocaloric, whereas the remaining were not. Comparator diets were defined as high carbohydrate and/or low fat or as according to standard diabetes guidelines with calorie restriction. The RCT of Tay et al. was the largest in terms of participants included.

All but one RCT found no effect of advising low carbohydrate diets on systolic blood pressure compared with advising high carbohydrate diets. However, the reported confidence intervals were rather wide. Based on this, the Committee notes it cannot be completely excluded that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed by Huntriss et al.[9]

Substitution by protein or fat

Where reported, the RCTs all advised substituting the carbohydrates in the (very) low carbohydrate diet with a combination of fat (MUFA, or MUFA combined with PUFA or SFA) and protein. Subgroup analyses by protein or fat substitution were therefore not possible.

Retention rates

Retention rates ranged from 54 to 87% in the low carbohydrate diet groups and from 62 to 90% in the high carbohydrate diet groups. Particularly, the RCT of Goldstein et al.[61] had relatively high numbers of dropouts, and there were more dropouts in the intervention group. However, the study was rather small in terms of numbers of participants included, and is likely to only minimally have impacted the overall conclusion.

Risk of bias

Huntriss et al.[9] did not present study-specific risk of bias assessments but reported that, in general, the risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.

Publication bias

Huntriss et al.[9] did not assess for presence of publication bias.

Dietary compliance

Achieved intakes in the two very low carbohydrate diet interventions were higher than prescribed, and in line with a low carbohydrate diet. Achieved intakes in the low carbohydrate diet interventions were (slightly) higher than prescribed and within the range of a low carbohydrate diet or slightly above. The lower compliance may have contributed to the lack of effect on systolic blood pressure.

Summary

RCTs that addressed the effects of advising low compared with high carbohydrate diets found no effect on systolic blood pressure, with minor heterogeneity between studies. However, the reported confidence intervals were rather wide, and based on that, it cannot be completely excluded that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure. Some of the included RCTs had moderate retention rates but this is unlikely to have affected the overall conclusion as indicated by the minor level of heterogeneity between studies. Achieved intakes in the low carbohydrate diet groups were (slightly) higher than prescribed, particularly for the very low carbohydrate diets.

Moderate carbohydrate diets

Study characteristics and main effects

The MA of Korsmo-Haugen et al.[18] was included in the evaluation. Study durations were 12 to 24 months for the RCTs included by Korsmo-Haugen et al. The MA included five moderate, two low, and one very low carbohydrate diet interventions. There was no heterogeneity between studies included in the MA, and therefore, the Committee judged the evidence applicable to moderate carbohydrate diets. The RCT of Larsen et al.[35] had

the largest weight in the MA. In the RCTs, participants were generally recommended to reduce body weight and/or energy intake. Four out of the 5 moderate carbohydrate diet RCTs were isocaloric. The comparator diets were defined as high carbohydrate, low fat, and low or standard protein.

The Committee additionally evaluated one RCT, of Esposito et al.[60], included in the MA of Huntriss et al.[9] The other moderate carbohydrate diet interventions included in the MA of Huntriss et al. were already included in the MA of Korsmo-Haugen et al. The RCT of Esposito et al. had a duration of 48 months. The intervention diet was a Mediterranean diet that was moderate in carbohydrates and the comparator diet was defined as a low fat, high carbohydrate diet. The advised diets were isocaloric.

The MA of Korsmo-Haugen et al. found no statistically significant effects of advising moderate carbohydrate diets on systolic blood pressure compared with high carbohydrate diets, without heterogeneity between studies. Contrarily to this MA, Esposito et al. found statistically significantly greater reductions in blood pressure among those who followed a moderate carbohydrate diet compared with control. Given that the RCT of Esposito et al. advised a Mediterranean diet to the low carbohydrate diet group, and that the achieved carbohydrate intakes in the intervention and control groups were very comparable, the effect on systolic blood pressure may be attributable to the Mediterranean diet rather than the carbohydrate restriction.

Subgroup and sensitivity analyses

No relevant subgroup analyses were performed by Korsmo-Haugen et al.[18]

Substitution by protein or fat

In total, four RCTs advised substituting the carbohydrates of the moderate carbohydrate diet with protein, and two with fat, specifically (M)UFA. The types of protein were not specified. Results are shown in Table 27. Given that the majority of studies advised protein substitutions, a comparison of effects with fat substitutions was not feasible.

Table 27 Long-term effects of advising moderate carbohydrate diets compared with high carbohydrate diets on systolic blood pressure (mmHg): RCTs with substitutions for protein and fat.

RCT	Substitution	Mean difference (95%CI) in systolic blood pressure (mmHg)
Wolever, 2008[26]	Fat	-1.53 (-3.93, 0.87)
Esposito, 2009[60]	Fat	-3.10 (-3.79, -2.23)
Brinkworth, 2004[47]	Protein	-0.60 (-9.30, 8.10)
Krebs, 2012[34]	Protein	1.70 (-3.38, 6.78)
Larsen, 2011[35]	Protein	-4.26 (-8.80, 0.28)
Pedersen, 2014[48]	Protein	-6.30 (-13.92, 1.32)

CI: confidence interval; RCT: randomised controlled trial.

Retention rates

Retention rates ranged from 56 to 91% in the moderate carbohydrate diet groups, and from 61 to 91% in the high carbohydrate diet groups. Particularly, in the RCT of Brinkworth et al.[47], retention rates were low. However, given the lack of heterogeneity between studies, it is not expected this impacted the overall conclusion.

Risk of bias

In the MA of Korsmo-Haugen et al.[18], none of the RCTs were scored as high risk of bias. In the MA of Huntriss et al.[9], no study-specific risk of bias assessments was presented. Huntriss et al. reported that the risk of bias was high in the majority of included studies due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention. Given the lack of heterogeneity between the RCTs included in the MA, it is not expected that this impacted the overall conclusion. Korsmo-Haugen et al. reported the overall quality of the evidence for combined low and moderate carbohydrate diets and combined short and long-term studies. It was graded as moderate quality of evidence since the majority of studies were scored as high or unclear risk of bias.

Publication bias

Korsmo-Haugen et al.[18] did assess publication bias for combined low and moderate carbohydrate diets and combined short and long-term studies, and reported there was no evidence for publication bias.

Dietary compliance

For the moderate carbohydrate diet interventions, achieved intakes were generally in line with the prescribed intakes. For the RCTs of Esposito et al.[60], Krebs et al.[34], Larsen et al.[35] and Pedersen et al.[48], achieved intakes of carbohydrates in the comparator groups were lower than advised, making the contrasts in intake between intervention and control groups smaller.

Summary

The MA of Korsmo-Haugen et al.[18] showed no difference in effect of advising moderate compared with high carbohydrate diets on systolic blood pressure. However, the reported confidence intervals were rather wide, and based on that, it cannot be completely excluded that advising low compared with high carbohydrate diets increases or decreases systolic blood pressure. There was no heterogeneity between the studies. The RCT of Esposito et al.[60] did not confirm this. However, this may be due to other aspects of the diet than the carbohydrate content. Some studies had moderate retention rates but it is not expected to have had a major impact on the conclusions due to the lack of heterogeneity between studies. Compliance with the moderate carbohydrate diet was good overall. In some RCTs, the contrast in achieved carbohydrate intakes between intervention and control groups was small, which may have contributed to the lack of effect.

3.7 Estimated glomerular filtration rate

The Committee used the MA of Suyoto et al.[19] for the evaluation of the effects of advising low and moderate carbohydrate diets on eGFR. The MA included 4 RCTs, of which two evaluated the effects of advising low carbohydrate diets. One of those evaluated short-term effects and one longer-term effects. Two of the RCTs evaluated the effects of advising moderate carbohydrate diets, of which one in the short term and one in the longer term. The results and characteristics are summarised in Table 28. In addition, Table 29 summarises results and characteristics of a recently published individual RCT regarding long-term effects of low carbohydrate diets on eGFR. The evaluated RCTs provided too little evidence for the Committee to base its conclusion on considering separate effects of short and longer-term effects and separate effects of advising low and moderate carbohydrate diets. Therefore, the Committee did not further evaluate the quality of the evidence of those studies.

Table 28 Summary of low and moderate carbohydrate diets and the short and long-term effects on eGFR in people with type 2 diabetes: meta-analysis of RCTs.

Meta-analysis; Study duration	Suyoto, 2018[19]; 3 weeks to 12 months
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: ≤43 en%; c: No cut off. Carbohydrate intake should be lower in i than c.
Number of studies; total number of participants	4 RCTs; 189
Number of studies according to category of carbohydrate restriction and study duration	Very low: 0 Low: 2; 1 short and 1 long term Moderate: 2; 1 short term and 1 long term
Heterogeneity	No: 0%
Strength of the effect: Standardised mean difference[a] (95%CI)	0.26 (-0.03, 0.55)
Study population	People diagnosed with type 2 diabetes; men and women; overweight and obese; diabetes medications[b]: oral agents, insulin; Europe, Australia, Japan

CI: confidence interval; eGFR: estimated glomerular filtration rate; RCT: randomised controlled trial;

[a] The standardised mean difference is calculated by dividing the difference between the mean difference of two groups by the pooled standard deviation.

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that *all* participants used those medications).

Table 29 Summary of low carbohydrate diets and the longer term effects on eGFR: individual RCT.

RCT; Study duration	Tay, 2018[15]; 24 months
Category of carbohydrate restriction	Low
Prescribed carbohydrate quantity of intervention (i) and control (c) group	i: 14 en%; c: 53 en%
Number of participants in intervention (i) and control (c) group	i: 58; c: 57
Strength of the effect: Mean difference (95%CI)[a]	-1 (-4, 2) ml/min/1.73m^2
Study population	People diagnosed with type 2 diabetes; diabetes duration[b]:7 years; men and women; BMI: 35 kg/m^2; diabetes medications[c]: oral agents insulin; Australia

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; RCT: randomised controlled trial.

[a] Values are the differences in estimated marginal mean changes between low and high carbohydrate diet groups, derived from a mixed effects linear regression model;

[b] BMI and Diabetes duration values represent the average in the study population;

[c] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

The Committee concluded the following:

Short and longer-term effects; low and moderate carbohydrate diets: There is too little research to draw conclusions regarding the effects of advising low or moderate carbohydrate diets compared with advising diets high in carbohydrates on eGFR in the short term or longer term, in people diagnosed with type 2 diabetes.

3.8 Impact of a recent meta-analysis on conclusions

In January 2021, an MA was published on the effects of low carbohydrate diets in people with type 2 diabetes.[21] This MA was published after the literature search and evaluation of the Committee were finalised. However, the Committee deemed the new MA of importance, and therefore decided to additionally evaluate the impact of the findings of this MA on its conclusions. Below, the MA is described. Next, the Committee explained if and how the findings of this MA impacted its conclusions drawn in the above Sections (3.2 to 3.7).

The MA published by Goldenberg et al.[21] was focused on the effects of (very) low carbohydrate compared with higher carbohydrate diets in people with type 2 diabetes. Low carbohydrate diets were defined as diets with <26 en% or <130 g/d carbohydrates, which is similar to the definition used by the Committee. Moderate carbohydrate diets were not evaluated in the MA. Outcomes evaluated in the MA, and relevant for the evaluation

of the Committee, were HbA1c, fasting glucose, body weight, LDL cholesterol at 6 and 12 months and remission of diabetes at 12 months. Remission of diabetes was not evaluated in the previously published MA. Goldenberg et al. requested unpublished data from the RCT authors with respect to HbA1c and use of medication in order to estimate diabetes remission. For 5 RCTs, such additional data were obtained. It was not reported which RCTs it concerned. Articles published until 25 August 2020 were included using a systematic search in multiple literature databases.

The MA of Goldenberg et al. included 23 RCTs, of which five were outside the inclusion criteria of the Committee. More specifically, two RCTs were described in conference abstracts rather than peer reviewed articles[62,63], two RCTs included an intervention of low carbohydrate diets plus other lifestyle changes such as the level of physical activity[64,65], and one RCT included a study population of combined non-diabetics and diabetics[66]. Those five RCTs were not included in the previously published MA that were used for the Committee's evaluation.

The MA of Goldenberg et al. furthermore included two recent, small-scale RCTs, that were not evaluated in the previously published MA that were used for the Committee's evaluation, and neither were found in the Committee's search for recent RCTs.[67,68] The remaining RCTs in the MA of Goldenberg et al. were already included in one or multiple previously published MA. However, the previously selected MA per health outcome by the Committee did not always include all the available RCTs. This is due to differences in inclusion criteria and selected health outcomes per MA. For instance, fasting plasma glucose was included as an outcome in the MA of van Zuuren et al.[10], but not in the other MA. The MA of van Zuuren et al. was based on RCTs that substituted carbohydrates with fat, and thus did not include RCTs that substituted carbohydrates with protein. These latter groups of RCTs were thus not included in the Committee's evaluation of fasting plasma glucose.

The level of heterogeneity (such as forest plots and/or I^2) between the studies included in the MA of Goldenberg et al. was presented for only a selection of the evaluated outcomes. GRADE assessments were performed to evaluate the level of certainty of the evidence for all the given outcomes above, except LDL cholesterol. A high level of heterogeneity between studies was a reason for Goldenberg et al. to downgrade the level of certainty of the evidence regarding the short-term effects on body weight and fasting glucose in the GRADE assessments. The Committee, therefore, assumes that, for outcomes where such downgrading due to heterogeneity was not reported, the level of heterogeneity was low or moderate. For LDL cholesterol, this assumption was not made since there was no GRADE assessment available for this outcome.

Below the findings per health outcome and the impact of those findings on the Committee's conclusions are described.

HbA1c

Short-term effects

The Committee concluded the following, as described in Section 3.2: "Intervention studies show that advising low carbohydrate diets compared with advising diets high in carbohydrate reduces HbA1c with 4.0 to 5.4 mmol/mol [0.36 to 0.49%] within 3 to 6 months, in people diagnosed with type 2 diabetes. The evidence is strong". The conclusion was based on evidence from 10 RCTs.

The findings of the new MA were as follows: in total, 17 RCTs were used for the 6-month analyses, with a total of 747 participants. The evaluation included two reports of conference abstracts, and two RCTs with interventions of combined low carbohydrate diets and other lifestyle changes. Participants that were advised to consume low carbohydrate diets had a 0.47% (95%CI: 0.34, 0.60) greater reduction in HbA1c than participants advised to consume diets higher in carbohydrates after 6 months follow-up. The extent of heterogeneity was not reported. The level of certainty of the evidence according to GRADE was scored as high.[21]

Conclusion: The MA finding is in line with the Committee's conclusion. Therefore, the Committee sees no reason to change its conclusion based on this newly published evidence.

Longer-term effects

The Committee concluded the following, as described in Section 3.2: "Intervention studies show there is likely no difference in effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on HbA1c within 12 to 24 months, in people diagnosed with type 2 diabetes." The conclusion was based on evidence from 7 RCTs.

The findings of the new MA were as follows: A total of 8 RCTs were used for the 12-month analyses, with a total of 489 participants. It was not reported which RCTs contributed to the MA. The extent of heterogeneity was not reported either. The MA found that the effect on HbA1c attenuated in the longer term, with a mean difference in change of HbA1c of 0.23% (95%CI: 0, 0.46). The level of certainty of the evidence according to scoring with GRADE was "moderate" since the 95%CI includes a small effect, no effect, and small worsening. The effect estimate found in the MA is borderline statistically significant, and higher than in the MA used in the Committee's evaluation. Since it is unknown which RCTs contributed to the MA of Goldenberg et al., it is difficult to explain those differences. However, the conclusion that the effect on HbA1c attenuates over time was observed in both evaluations.[21]

Conclusion: The MA finding is in line with the Committee's conclusion. Therefore, the Committee sees no reason to change their conclusion based on this newly published evidence.

Body weight

Short-term effects

The Committee concluded the following, as described in Section 3.3: "Intervention studies show that advising low carbohydrate diets compared with diets high in carbohydrates, reduces body weight by approximately 2.5 kg in people diagnosed with type 2 diabetes after 3 months. The evidence is strong." This is based on evidence from 5 RCTs.

And: "Intervention studies show there is likely no difference in effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on body weight after 6 months, in people diagnosed with type 2 diabetes." This is based on evidence from 8 RCTs.

The findings of the new MA were as follows: In total, 18 RCTs were used for the 6-month (short-term) analyses, with a total of 882 participants. Participants that were advised to consume low carbohydrate diets had a 3.46 (95%CI: 1.67, 5.35) kg greater reduction in body weight than participants advised to consume diets higher in carbohydrates after 6 months follow-up. There was 63% heterogeneity. The level of certainty of the evidence according to GRADE was scored as moderate, particularly due to suggestive publication bias. After splitting the studies into low risk of bias versus studies at high risk of bias or with some concerns, there remained heterogeneity among the studies at high risk of bias or with some concerns (57%). There was no heterogeneity among the studies at low risk of bias (n=6), and the mean difference in body weight change was -7.41 (-9.75 to -5.08) kg. This effect was to a large extent driven by two RCTs that evaluated an intervention of combined low carbohydrate diets and other lifestyle changes. The remaining four studies found no statistically significant difference in effect on body weight change, which is in line with the Committee's conclusion of no difference in effect at 6 months.[21]

Conclusion: The MA finding is in line with the Committee's conclusion. Therefore, the Committee sees no reason to change their conclusion based on this newly published evidence.

Longer-term effects

The Committee concluded the following, as described in Section 3.3: "Intervention studies show there is likely no difference in effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on body weight within 12 to 24 months, in people diagnosed with type 2 diabetes." This is based on evidence from 6 RCTs.

The findings of the new MA were as follows: A total of 7 RCTs were used for the 12-month analyses, with a total of 499 participants. The evaluation included one report of an RCT with combined diabetics and non-diabetics in the study population. The MA found no difference in effect on body weight change between advising low and higher carbohydrate diets (mean difference 0.29 kg (95%CI: -1.02, 1.60)). The extent of heterogeneity was

not reported. The level of certainty of the evidence according to scoring with GRADE was “moderate”. The analysis for publication bias was under-powered. Since publication bias was suggested for the 6-month MA on body weight, the authors cautiously rated down their GRADE assessment to “moderate” for the 12-month MA.[21]

Conclusion: the MA finding is in line with the Committee’s conclusion. Therefore, the Committee sees no reason to change their conclusion based on this newly published evidence.

Fasting plasma glucose

Short-term effects

The Committee concluded the following, as described in Section 3.4: “Intervention studies show that advising low carbohydrate diets compared with advising diets high in carbohydrate reduces fasting plasma glucose within 4 to 6 months, in people diagnosed with type 2 diabetes. The evidence is limited.” This is based on evidence from 4 RCTs.

The findings of the new MA were as follows: A total of 14 RCTs were used for the 6-month analyses, with a total of 611 participants. The evaluation included two conference abstracts, one RCT with an intervention of a combined low carbohydrate diet and other lifestyle changes, and an RCT with a study population of combined non-diabetics and diabetics. Participants that were advised to consume low carbohydrate diets had a 0.73 mmol/L (95%CI: 0.27, 1.19) greater reduction in fasting glucose than participants advised to consume diets higher in carbohydrates after 6 months follow-up. However, there was a large amount of unexplained heterogeneity (I^2 68%, P<0.001). The level of certainty of the evidence according to scoring with GRADE was “moderate” because of this hetero-geneity.[21]

The Committee noted the number of RCTs contributing to the new MA differed substantially from their evaluation. This is likely explained as follows: the Committee used the MA of van Zuuren et al.[10] for the evaluation of effects on fasting glucose. That MA only included RCTs that evaluated carbohydrate-fat substitutions, which likely yielded a relatively lower number of studies in the evaluation. The other MAs included in the evaluation of the Committee did not include fasting glucose data. Despite the difference in numbers of RCTs included, the conclusions of a reducing effect on fasting glucose are similar between the two evaluations. Also, both found that the effects were not fully homogeneous, which contributed to the conclusion of a limited level of evidence (instead of strong).

Conclusion: The MA finding is in line with the Committee’s conclusion. Therefore, the Committee sees no reason to change their conclusion based on this newly published evidence.

Longer-term effects

The Committee concluded the following, as described in Section 3.4: "There is too little research to draw conclusions regarding the effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on fasting plasma glucose within 12 to 24 months, in people diagnosed with type 2 diabetes." This is based on evidence from 2 RCTs.

The findings of the new MA were as follows: A total of 6 RCTs were used for the 12-month (long-term) analyses, with a total of 365 participants. The evaluation included two RCTs that were also included by the Committee for its evaluation, and two RCTs that fell outside the inclusion criteria of the Committee (one with combined diabetics and non-diabetics in the study population, and one with 6-month instead of 12-month follow-up). The extent of heterogeneity was not reported. There was no difference in the effect of advising low compared with higher carbohydrate diets on fasting glucose, with a mean difference of 0.06 mmol/L (95%CI: -0.37, 0.48). The level of certainty of the evidence according to scoring with GRADE was "moderate" since the 95%CI includes a small effect, no effect, and small worsening. This MA finding differs from the Committee's conclusion.[21]

Of the 6 RCTs included in the MA, two RCTs were inside the inclusion criteria of the Committee and not yet part of its evaluation.[61,69] Both RCTs did not find differences in effects on fasting glucose levels. Of the two RCTs already included in its evaluation[15,50], one found a reducing effect and one found no effect of low carbohydrate diets on fasting glucose levels, leading to heterogeneous findings. According to the approach used by the Committee (see decision tree; Annex L), the situation of 4 RCTs with inconsistent findings leads to the conclusion there is too little research to draw a conclusion. The Committee therefore concluded that, had those two additional RCTs been taken into account in the Committee's evaluation, its conclusion would not have changed.

Conclusion: Adding the two additional studies from the MA would not change the Committee's conclusion.

LDL cholesterol

Short-term effects

The Committee concluded the following, as described in Section 3.5: "Intervention studies show there is likely no difference in effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on LDL cholesterol within 3 to 6 months, in people diagnosed with type 2 diabetes." This is based on evidence from 7 RCTs.

The findings of the new MA were as follows: A total of 15 RCTs were used for the 6-month (short-term) analyses, with a total of 672 participants. It was not reported which RCTs contributed to the MA. The extent of hetero-

geneity was not reported either. There was no difference in effect of advising low compared with higher carbohydrate diets on LDL cholesterol, with a mean difference of 0.02 mmol/L (95%CI: -0.09, 0.12). The level of certainty of the evidence according to scoring with GRADE was “high”.[21]

Conclusion: The MA finding is in line with the Committee’s conclusion. Therefore, the Committee sees no reason to change their conclusion based on this newly published evidence.

Longer-term effects

The Committee concluded the following, as described in Section 3.5: “Intervention studies show there is likely no difference in effects of advising low carbohydrate diets compared with advising diets high in carbohydrates on LDL cholesterol within 12 to 24 months, in people diagnosed with type 2 diabetes.” This is based on evidence from 7 RCTs. The Committee also noted it is expected that particularly the subgroups of fat used in the substitution of carbohydrates will impact LDL cholesterol levels.

The findings of the new MA were as follows: a total of 6 RCTs were used for the 12-month (long-term) analyses, with a total of 429 participants. It was not reported which RCTs contributed to the MA. The extent of heterogeneity was not reported either. Participants that were advised to consume low carbohydrate diets had 0.14 mmol/L (95%CI: -0.00, 0.28) greater increases in LDL cholesterol than participants advised to consume diets higher in carbohydrates after 6 months follow-up. This was borderline statistically significant, and the authors concluded that low carbohydrate diets may be potentially harmful with respect to LDL cholesterol. The level of certainty of the evidence according to scoring with GRADE was “moderate”. No explanation for this judgement was given.[21]

Although the Committee did not find evidence for an LDL-increasing effect of low carbohydrate diets, the Committee acknowledged that it is crucial to take into account the type of fat used as a substitute for the carbohydrates in the low carbohydrate diet. Based on RCTs performed in the general population, it is known that substitution of carbohydrates with saturated fat can increase LDL cholesterol levels. Since it is unknown which RCTs contributed to Goldenberg’s MA of LDL cholesterol, it was not possible for the Committee to verify whether this explains the LDL cholesterol-raising effect in Goldenberg’s MA.

Conclusion: The MA finding is in line with the Committee’s conclusion. Therefore, the Committee sees no reason to change its conclusion based on this newly published evidence.

Diabetes remission

None of the MA used by the Committee included data on diabetes remission. The Committee defined diabetes remission as HbA1c <48 mmol/mol and no use of diabetes medication for at least one year. In the MA of Goldenberg et al., there was no effect of low compared with higher carbohydrate diets on diabetes remission (RR 0.79 [95%CI: 0.36, 1.73]), based on 2 RCTs with 126 participants. The level of certainty of the evidence according to scoring with GRADE was “low”. This was due to imprecision (the optimal information size was not achieved, and the confidence interval was very wide). It was not reported which RCTs contributed to the MA.[21] According to the approach taken by the Committee, two RCTs is too few to base conclusions on. Therefore, the Committee did not add those studies to its evaluation.

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annexes

A different forms of reduced carbohydrate diets

Feinman et al.[4] suggested the following definitions for reduced carbohydrate diets:

- **Very low carbohydrate diet or ketogenic diet**
  Very low: 20 to 50 grams per day (g/d); ≤10 en%;
  Derived from levels of carbohydrates required to induce ketosis in post people.
- **Low carbohydrate diet**
  >50 to <130 g/d; >10 to <26 en%;
  The recommended minimum intake according to the American Diabetes Association (130 g/d).
- **Moderate carbohydrate diet**
  130 to 230 g/d; 26 to 45 en%;
  The upper limit of carbohydrate intake before the obesity epidemic (43% en%).
- **High carbohydrate diet**
  >230 g/d; >45 en%;
  The recommended target according to the American Diabetes Association (45 to 65 en%).

B search strategy and flow of literature search

Articles selected by SACN working group as starting point

The SACN working group searched SR with MA published until September 2018.[8] In total, 8 SRs with MAs (Naude et al.[70], 2014; Fan et al.[71], 2016; Meng et al.[72], 2017; Snorgaard et al.[73], 2017; Huntriss et al.[9], 2018; Korsmo-Haugen et al.[18], 2018; Sainsbury et al.[5], 2018; van Zuuren et al.[10], 2018) and 1 network MA (Schwingshackl et al.[74], 2018) were included for further consideration. After further assessment, only results from 4 SRs with MAs (Huntriss et al., 2018; Korsmo-Haugen et al., 2018; Sainsbury et al., 2018; van Zuuren et al., 2018) were prioritised and used to grade the evidence and draw conclusions. This is because these publications were more recent, larger (in terms of number of participants) and considered to be of better quality than the older SRs with MAs (Naude et al., 2014; Fan et al., 2016; Meng et al., 2017; Snorgaard et al., 2017). The network MA was also not considered further since it included mainly indirect comparisons and did not provide any additional information to that obtained from the SRs with MAs of direct comparisons between lower and higher carbohydrate intakes[8].

The Committee used the 4 SRs with MAs selected by the SACN working group as starting point for their selection of relevant scientific literature.

Meta-analyses and systematic reviews

The Committee used the following searches on 3 (Scopus) and 8 (PubMed) June 2020 to find more recent SRs/MAs and SRs/MAs with additional outcomes not reported by the SACN working group:

PubMed

((Diet, Carbohydrate-Restricted[Mesh] OR diet, carbohydrate restricted[tiab] OR diet, low carbohydrate[tiab] OR Diet, low-carbohydrate[tiab] OR diet, carbohydrate-restricted[tiab] OR Low-Carbohydrate Diet*[tiab] OR Carbohydrate Restricted Diet*[tiab] OR carbohydrate restriction[tiab] OR carbohydrate quantity[tiab]) AND Diabet* AND (Systematic review[publication type] OR systematic review[tiab] OR Meta-analysis[publication type] OR Meta-analysis[tiab]))

Scopus

TITLE-ABS-KEY (“Meta-analysis”) OR TITLE-ABS-KEY (“Systematic review”) AND TITLE-ABS-KEY (“Diet,Carbohydrate-Restricted”) OR TITLE-ABS-KEY (“diet,low carbohydrate”) OR TITLE-ABS-KEY (“diet,carbohydrate-restricted”) OR TITLE-ABS-KEY (“Low-Carbohydrate Diet*”) OR TITLE-ABS-KEY (“Carbohydrate Restricted Diet*”) OR

TITLE-ABS-KEY (“carbohydrate restriction”) OR TITLE-ABS-KEY (“carbohydrate quantity”) AND TITLE-ABS-KEY (“Diabet*”)

In PubMed, 48 articles were found. In Scopus, 308 articles were found. After removing duplicates, 327 articles were left for title and abstract screening. From those 327 articles, 6 more recent articles were selected for full text screening. After full text screening, one recent SR with MA was selected (McArdle et al., 2019 [11]). The remaining were excluded, particularly since articles did not perform MA or included RCTs that were already covered in the previously selected SR with MA articles.

In addition, from the 327 articles, 12 were selected for full text screening because of potential additional endpoints (either because these were suggested in the abstract or because there was no abstract available). After full text screening, one SR with MA was selected (Soyuto et al.[19], 2018) that reported on eGFR as outcome. The remaining were excluded, particularly since those were not SRs and MAs, since they did not report on additional outcomes or included RCTs that were already covered in the previously selected SRs with MAs.

Taken together, the Committee selected the following 6 MAs:

- Huntriss et al.[9], 2018
- Korsmo-Haugen et al.[18], 2018
- Sainsbury et al.[5], 2018
- van Zuuren et al.[10], 2018
- McArdle et al.[11], 2019
- Soyuto et al.[19], 2018

Randomised controlled trials

In addition, RCTs published after the inclusion date of the most recent SR with MA were searched using the following searches on 18 (Scopus) and 22 (PubMed) June 2020:

PubMed

((Diet, Carbohydrate-Restricted[Mesh] OR diet, carbohydrate restricted[tiab] OR diet, low carbohydrate[tiab] OR Diet, low-carbohydrate[tiab] OR diet, carbohydrate-restricted[tiab] OR Low-Carbohydrate Diet*[tiab] OR Carbohydrate Restricted Diet*[tiab] OR carbohydrate restriction[tiab] OR carbohydrate quantity[tiab] OR Diet, Ketogenic[Mesh] OR Diet, Ketogenic[tiab] OR Low-Carbohydrate Ketogenic Diet[tiab]) AND Diabet* AND (Clinical trial[publication type] OR clinical trial[tiab] OR randomized trial[tiab] OR intervention study[tiab]))

Limit 2017

Scopus

((TITLE-ABS-KEY (*"Diet,Carbohydrate-Restricted"*) OR TITLE-ABS-KEY (*"Diet,low-carbohydrate"*) OR TITLE-ABS-KEY (*"diet,carbohydrate-restricted"*) OR TITLE-ABS-KEY (*"Low-Carbohydrate Diet*"*) OR TITLE-ABS-KEY (*"Carbohydrate Restricted Diet*"*) OR TITLE-ABS-KEY (*"carbohydrate restriction"*) OR TITLE-ABS-KEY (*"carbohydrate quantity"*) OR TITLE-ABS-KEY (*"Diet,Ketogenic"*) OR TITLE-ABS-KEY (*"Low-Carbohydrate Ketogenic diet"*))) AND (TITLE-ABS-KEY (*diabet**)) AND ((TITLE-ABS-KEY (*"Clinical trial"*) OR TITLE-ABS-KEY (*"randomized trial"*) OR TITLE-ABS-KEY (*"intervention study"*))) AND (LIMIT-TO (PUBYEAR , *2020*) OR LIMIT-TO (PUBYEAR , *2019*) OR LIMIT-TO (PUBYEAR , *2018*) OR LIMIT-TO (PUBYEAR , *2017*))

In PubMed, 49 articles were found. In Scopus, 72 articles were found. After removing duplicates, 97 articles were left for title and abstract screening. From those 97, 12 articles were selected based on title and abstract for full text screening. Of those, 6 were selected to be used for the current evaluation. Reasons for exclusion were that RCTs were already covered in the SRs with MAs, had unclear or incorrect definitions of the reduced carbohydrate diets or did not include relevant study outcomes.

It concerns the following articles:

- Liu et al.[12], 2018
- Wang et al.[13], 2018
- Saslow et al.[14], 2017
- Tay et al.[15], 2018
- Sato et al.[16], 2017
- Struik et al.[17], 2020

Selection of articles per outcome

Below a description of the selection process per health outcome is given.

HbA1c and body weight

Five MAs (Huntriss et al.[9], 2018; Korsmo-Haugen et al.[18], 2018; Sainsbury et al.[5], 2018; van Zuuren et al.[10], 2018; McArdle et al.[11], 2019) provided outcome data on HbA1c and body weight. Of those, one MA, of Sainsbury et al., separated MA effects by both study duration (short versus long term) and extent of carbohydrate restriction (low versus moderate). Therefore, this MA was selected by the Committee for the evaluation of short and long term effects of low and moderate carbohydrate diets. The MA included the following number of RCTs for the HbA1c and body weight outcomes:

- Short term – low carbohydrate diets: 7 (HbA1c); 6 (body weight)
- Short term – moderate carbohydrate diets: 11 (HbA1c) 10 (body weight)
- Longer term – low carbohydrate diets: 7 (HbA1c); 6 (body weight)
- Longer term – moderate carbohydrate diets: 8 (HbA1c); 7 (body weight)

In addition, the MA of McArdle et al. was selected for the evaluation of short term effects of low carbohydrate diets on HbA1c (5 RCTs) and body weight (5 RCTs). The MA of McArdle et al. separated very low, low and moderate carbohydrate diet studies. Initially, McArdle et al. did not separate results based on study durations. However, since all RCTs in the subgroup analyses of low carbohydrate diets were of 6 month or shorter duration, the findings of low carbohydrate diet studies were of use for the evaluation of short term effects on HbA1c and body weight. This MA included 5 RCTs of which 3 were not yet covered by Sainsbury et al.
In addition, 5 recent RCTs (Liu et al.[12], 2018; Wang et al.[13], 2018; Saslow et al.[14], 2017; Tay et al.[15], 2018; Sato et al.[16], 2017) provided evidence on HbA1c outcomes, and 4 recent RCTs (Struik et al.[17], 2020; Saslow et al., 2017; Tay et al., 2018; Sato et al., 2017) on body weight outcomes. Those were included as well.

Fasting plasma glucose

One MA (van Zuuren et al.[10], 2018) provided outcome data on fasting plasma glucose. A distinction was made in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). Given that no alternative MAs were available that separated effects by both aspects, the Committee selected the MA of van Zuuren et al. for the evaluation of effects of reduced carbohydrate diets on fasting plasma glucose. There were 4 (very) low carbohydrate diet studies and 1 moderate carbohydrate diet studies included in the MA regarding short term effects. Regarding longer term effects, there were 1 low and 3 moderate carbohydrate diet studies included in the MA. Since heterogeneity was present between studies included in both the short and long term MA, forest plots presenting the effects of the included RCTs were added, with marked low and moderate carbohydrate diet interventions, to allow separate conclusions on effects of advising low and

moderate carbohydrate diets. In addition, two recent RCTs (of Liu et al.[12], 2018; Wang et al.[13], 2018) provided evidence regarding effects of advising moderate carbohydrate diets on fasting glucose outcomes in the short term. One recent RCT (of Tay et al.[15], 2018) provided evidence regarding effects of advising low carbohydrate diets on fasting plasma glucose. Those were included as well.

LDL cholesterol

Five MAs (Huntriss et al.[9], 2018; Korsmo-Haugen et al.[18], 2018; Sainsbury et al.[5], 2018; van Zuuren et al.[10], 2018; McArdle et al.[11], 2019) provided outcome data on LDL cholesterol. Two of those only qualitatively assessed the evidence (Sainsbury et al. and McArdle et al.) and were therefore discarded. Of the remaining three MAs (Huntriss et al., 2018; Korsmo-Haugen et al., 2018; van Zuuren et al., 2018), the following were selected:

For the evaluation of short term effects of advising low carbohydrate diets:
The MA of van Zuuren et al.[10] was selected since this MA specifically investigated effects of advising low carbohydrate diets. The MA included 5 RCTs. In addition, the MA of and Korsmo-Haugen et al.[18] was also selected. This MA made a distinction in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). Since heterogeneity was present between the included studies, forest plots presenting the effects of the included RCTs were added, with marked low and moderate carbohydrate diet interventions, to allow separate conclusions on effects of advising low and moderate carbohydrate diets. Of the 3 low carbohydrate diet interventions, two were not yet covered by van Zuuren et al. The MA of Huntriss et al.[9] did not investigate short term effects and was therefore discarded.

For the evaluation of short term effects of advising moderate carbohydrate diets:
The above described MA of Korsmo-Haugen et al.[18], for the evaluation of short term effects of advising low carbohydrate diets, was selected for the evaluation of advising moderate carbohydrate diets. It included 3 RCTs on the effects of advising moderate carbohydrate diets. The MA of van Zuuren et al. was discarded since it evaluated low carbohydrate diets only. The MA of Huntriss et al.[9] did not investigate short term effects and was therefore discarded. One recently published RCT of Liu et al.[12] (2018) was also selected.

For the evaluation of long term effects of low carbohydrate diets:
The MA of Huntriss et al.[9] was selected. This MA made a distinction in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). However, there was no heterogeneity between studies and therefore the MA results were of use for the evaluation of both low and moderate carbohydrate diet advises. The MA of Huntriss et al. included 4 (very) low carbohydrate diet RCTs. The other

two MAs, of van Zuuren et al.[10] and Korsmo-Haugen et al.[18], were discarded since all low carbohydrate diet studies used in those two MAs were included in the MA of Huntriss et al. as well, plus additional RCTs, making the MA of Huntriss et al. the most complete MA. In addition, three recent individual RCTs were selected (Saslow et al.[14], 2017; Sato et al.[16], 2017; Tay et al.[15], 2018).

For the evaluation of long term effects of moderate carbohydrate diets:
The MA of Korsmo-Haugen et al.[18] was selected. This MA made a distinction in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). Since heterogeneity was present between the included studies, forest plots presenting the effects of the included RCTs were added, with marked low and moderate carbohydrate diet interventions, to allow separate conclusions on effects of advising low and moderate carbohydrate diets. The MA of Korsmo-Haugen et al. included 7 moderate carbohydrate diet RCTs. The other two MAs, of van Zuuren et al.[10] and Huntriss et al.[9] were discarded since all moderate carbohydrate diet studies used in those two MAs were included in the MA of Korsmo-Haugen et al. as well, plus additional RCTs, making the MA of Korsmo-Haugen et al. the most complete MA.

Systolic blood pressure

Five MAs (Huntriss et al.[9], 2018; Korsmo-Haugen et al.[18], 2018; Sainsbury et al.[5], 2018; van Zuuren et al.[10], 2018; McArdle et al.[11], 2019) provided outcome data on systolic blood pressure. Two of those only qualitatively assessed the evidence (Sainsbury et al. and McArdle et al.) and were therefore discarded. Of the remaining three MAs (Huntriss et al., 2018; Korsmo-Haugen et al., 2018; van Zuuren et al., 2018), the following were selected:

For the evaluation of short term effects of low and moderate carbohydrate diets:
The MAs of Korsmo-Haugen et al.[18] and van Zuuren et al.[10] were selected. The MA of Huntriss et al. did not investigate short term effects and was therefore discarded. Both MAs made a distinction in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). However, there was no heterogeneity between studies in both MAs and therefore the results of the MAs were of use for the evaluation of both low and moderate carbohydrate diets. The MA of Korsmo-Haugen included 6 RCTs, and the MA of van Zuuren et al. included 4 RCTs. There was only one RCT that overlapped between the MAs. One recent RCT, of Liu et al.[12], that addressed effects of advising moderate carbohydrate diets was included as well.

For the evaluation of long term effects of low carbohydrate diets:
The MA of Huntriss et al.[9] was selected. This MA made a distinction in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). Since heterogeneity was

present between the included studies, forest plots presenting the effects of the included RCTs were added, with marked low and moderate carbohydrate diet interventions, to allow separate conclusions on effects of advising low and moderate carbohydrate diets. The MA of Huntriss et al. included 5 (very) low carbohydrate diet RCTs. The MAs of van Zuuren et al.[10] and Korsmo-Haugen et al.[18] were discarded since all RCTs included in those MAs were already covered by Huntriss et al.

For the evaluation of long term effects of moderate carbohydrate diets:
The MAs of Korsmo-Haugen et al.[18] and Huntriss et al.[9] were selected. The MA of Korsmo-Haugen et al. included 5 moderate carbohydrate diet RCTs. The MA of Huntriss et al. included 2 moderate carbohydrate diet RCTs of which one overlapped with Korsmo-Haugen et al. The remaining RCT included by Huntriss et al. was included in the evaluation. Both MAs made a distinction in study duration (short versus long term), but not in the extent of carbohydrate restriction (low versus moderate). In the MA of Huntriss et al., heterogeneity was present between the included studies. Therefore, forest plots presenting the effects of the included RCTs were added, with marked low and moderate carbohydrate diet interventions, to allow separate conclusions on effects of advising low and moderate carbohydrate diets.

Estimated glomerular filtration rate
Two MAs (Sainsbury et al.[5], 2018 and Suyoto et al.[19], 2018) provided outcome data on estimated glomerular filtration rate. Sainsbury et al. only qualitatively assessed the evidence and was therefore discarded, leaving the MA of Suyoto et al. for the evaluation. That MA included 4 RCTs of low or moderate and short or longer duration. One additional RCT, of Tay et al.[15] was selected that evaluated low carbohydrate diets in the longer term.

C short-term RCTs on HbA1c and body weight

Table A2 Individual RCTs included in the evaluation of short-term effects of reduced carbohydrate diets on HbA1c and body weight: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA[a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Samaha, 2003[32] 6 months SA: HbA1c; 6%	[1] Low carbohydrate [2] Low fat	[1] 30 g [2] NR	[1] 22 [2] 51 6 months	[1] P: 37* F: 41* [2] P: 16* F: 30 Subtypes not reported	P&F	[1] 26; 17 (65%) [2] 26; 12 (46%)	ITT	SA: L
Saslow, 2014[24] 3 months SA: HbA1c; 9% Body weight: 7%	[1] very low carbohydrate. ketogenic, high fat, non-calorie restricted [2] moderate carbohydrate, calorie restricted, low fat	[1] 20-50 g [2] 45-50; 165 g	[1] 14; 58 g [2] 41; 139 g 3 months	[1] P: 24* F: 58* [2] P: 21* F: 35* Subtypes not reported.	P&F	[1] 16; 15 (94%) [2] 18; 17 (94%)	ITT	SA: L
Westman, 2008[31] 3; 6 months SA: HbA1c; 2%; 2% Body weight: 5%; 5%	[1] Low carbohydrate, ketogenic [2] Low GI, reduced calorie	[1] <20 g [2] 55	[1] 13; 49 g [2] 44; 149 g 6 months	[1] P: 28* F: 59* [2] P: 20* F: 36* Subtypes not reported.	P&F	[1] 38; 21 (55%) [2] 46; 29 (63%)	PP	SA: H
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Daly, 2006[27] 3 months SA: HbA1c; 8% Body weight; 10% McA: Hba1c; 4% Body weight; 5%	[1] Low carbohydrate [2] Low fat	[1] ≤ 70 g [2] NR	[1] 34; 110 g [2] 45; 169 g 3 months	[1] P: 26*; F: 40*; SFA: 14* [2] P: 21*; F: 33*; SFA: 11*	P&F, of which the majority UFA	[1] 51; 40 (78%) [2] 51; 39 (76%)	PP	SA: L McA: NR

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Davis, 2009[28] 3; 6 months SA: HbA1c; 7%; 10%; Body weight; 11%; 12%	[1] Low carbohydrate [2] Low fat	[1] 2 week phase of 20-25g, followed by a weekly increase of 5 g [2] NR	[1] 34 [2] 48 6 months	[1] P: 23*; F: 44*; SFA: 29*; PUFA: 18*; MUFA: 41* [2] P: 19*; F: 25; SFA: 30*; PUFA: 21*; MUFA: 38*	P&F, of which the majority MUFA & PUFA	[1] 55; 47 (85%) [2] 50; 44 (88%) 12 months	ITT	SA: U
Guldbrand, 2012[45] 6 months SA: HbA1c; 1%; Body weight; 11%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	[1] 25 [2] 49 6 months	[1] P: 30; F: 50; SFA: 19; PUFA: 6; MUFA: 16 [2] P: 10-15; F: 30; SFA < 10; PUFA: 5*; MUFA: 11	P&F, of which majority SFA and MUFA	[1] 30; 26 (87%) [2] 31; 28 (90%) 24 months	ITT	SA: L
Jonasson, 2014[29] 6 months McA: HbA1c; 4% Body weight; 5%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	[1] 25 [2] 49 6 months	[1] P: 23*; F: 49; SFA: 20*; PUFA: 8*; MUFA: 18* [2] P: 20*; F: 30; SFA 11*; PUFA: 5*; MUFA: 11*	P&F, of which majority SFA and MUFA	[1] 30; 30 (100%) [2] 31; 31 (100%) 6 months	NR	McA: NR
Jonsson, 2009[33] 6 months McA: HbA1c; 2% Body weight; 2%	[1] Paleolithic diet [2] The European Association for Diabetes recommendations	[1] NR [2] NR	[1] 32 [2] 42 6 months	[1] P: 24*; F: 39* [2] P: 34*; F: 20* Subtypes not reported.	P&F	[1; 2] 26; 26 (100%) 6 months	NR	McA: NR
Sato, 2017[30] 6 months McA: HbA1c; 4% Body weight; 5%	[1] Low carbohydrate [2] Calorie restricted	[1] 130 g [2] 50-60	[1] 44; 149 g [2] 49; 189 g 6 months	[1] P: 64*; F: 52*; SFA: 16*; PUFA: 11*; MUFA: 19* [2] P: 63*; F: 52*: SFA: 14*; PUFA: 11*; MUFA: 19*	None	[1] 33; 30 (97%) [2] 33; 32 (91%) 6 months	ITT	McA: NR
Struik, 2020[17] 4 months Individual RCT Body weight	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 14 [2] 50 6 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 41 (71%) [2] 57; 43 (75%) 4 months	ITT	L

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Yamada, 2014[52] 6 months SA: HbA1c; 7% Body weight; 5% McA: HbA1c; 3% Body weight; 3%	[1] Low carbohydrate [2] Conventional calorie-restricted	[1] 70-130 g [2] 50-60	[1] 30; 126 g [2] 51; 203 g 6 months	[1] P: 25*; F: 45* [2] P: <20 F: <25 Subtypes not reported.	P&F	[1] 12; 12 (100%) [2] 12; 12 (100%) 6 months	PP	SA: U McA: NR
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Brehm, 2009[38] 4; 8 months SA: HbA1c; 10%; 8% Weight; 9%; 10%	[1] High MUFA [2] High carbohydrate ISOCALORIC	[1] 45 [2] 60	[1] 46 [2] 54 12 months	[1] P: 15; F: 40; MUFA: 20 [2] P: 15; F: 25; MUFA: 9*	F; of which majority likely MUFA	[1] 62; 43 (69%) [2] 62; 52 (85%) 12 months	PP	SA: U
Brunerova, 2007[39] 3 months SA: HbA1c; 4% Body weight; 6%	[1] Hypocaloric, high-fat enriched with MUFA [2] Conventional diet ISOCALORIC	[1] 45 [2] 60	[1] NR [2] NR	[1] P: 10; F: 45; SFA: 11; PUFA: 11; MUFA: 23 [2] P: 10; F: 30; SFA 10; PUFA: 10; MUFA: 10	F; of which the majority MUFA	[1] 14; 14 (100%) [2] 13; 13 (100%) 3 months	NR	SA: H
Fabricatore, 2011[40] 5 months SA: HbA1c; 14%	[1] Low GL [2] Low fat ISOCALORIC	[1] NR [2] NR	[1] 41 [2] 50 9 months	[1] P: 20*; F: 40-60 g, dependent on kcal intake [2] P: 19*; F: ≤ 30 Subtypes not reported.	F	[1] 40; 24 (60%) [2] 39; 26 (67%) 9 months	ITT	SA: L
Krebs, 2012[34] 6 months SA: HbA1c; 17%; Body weight; 20%	[1] Low fat higher protein [2] Low fat higher carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 45 [2] 49 6 months	[1] P: 30; F: 30; SFA: 13* [2] P: 15: F: 30; SFA: 12*	P	[1] 207; 144 (70%) [2] 212; 150 (71%) 24 months	ITT	SA: L
Larsen, 2011[35] 3 months SA: HbA1c; 22%; Body weight; 13%	[1] High protein [2] High carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 40 [2] 49 3 months	[1] P: 30 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13 [2] P: 15 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13	P	[1] 53; 43 (81%) [2] 46; 37 (80%) 12 months	ITT	SA: L

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Liu, 2018[12] 3 months Individual RCT HbA1c Body weight	[1] Low carbohydrate [2] High carbohydrate, low protein, low omega-3 PUFA ISOCALORIC	[1] 42 [2] 54	[1] NR [2] NR 3 months	[1] P: 28 ; F: 30 [2] P: 17 ; F: 29 Subtypes not reported.	P	[1] 30; 26 (87%) [2] 30; 25 (83%) 3 months	ITT	L
Luger, 2013[36] 3 months SA: HbA1; 3% Body weight; 5%	[1] High protein [2] The European Association for Diabetes recommendations ISOCALORIC	[1] 40 [2] 55	[1] 38 [2] 50 3 months	[1] P: 30 ; F: 30 [2] P: 15 ; F: 30 Subtypes not reported.	P	[1] 22; 20 (91%) [2] 22; 22 (100%) 3 months	PP	SA: U
Parker, 2002[37] 3 months SA: HbA1c; 9% Body weight; 10%	[1] High protein [2] Low protein ISOCALORIC	[1] 40 [2] 60	[1] 43 [2] 55 3 months	[1] P: 30; F: 25; SFA: 8; PUFA: 5; MUFA: 12 [2] P: 15; F: 25; SFA: 8; PUFA: 5; MUFA: 12	P	[1] 36; 31 (86%) [2] 28; 23 (82%) 3 months	NR	SA: H
Wang, 2018[13] 3 months Individual RCT HbA1c	[1] Low carbohydrate [2] Low fat diet	[1] < 45 [2] NR	[1] 39 [2] 56 3 months	[1] P: 19*; F: 42* [2] P: 18*; F: 26* Subtypes not reported.	F	[1] 28; 24 (86%) [2] 28; 25 (89%) 3 months	ITT	Some concerns
Watson, 2016[41] 3&6 months SA: HbA1c; 5%; 6% Body weight; 7%; 4%	[1] High protein [2] High carbohydrate ISOCALORIC	[1] 33 [2] 51	[1] 34 [2] 47 6 months	[1]P: 32 F: 30; SFA <10; PUFA: 6*; MUFA: 13* [2]P: 22 F: 22; SFA <10; PUFA: 4*; MUFA: 10*	P&F, specifically MUFA and PUFA	[1] 32; 23 (72%) [2] 29; 21 (72%) 6 months	ITT	SA: U
Wolever, 2008[26] 3; 6 months SA HbA1c; 20%; 19% Body weight; 14%; 21%	[1] Low carbohydrate, high MUFA [2] Low GI, high carbohydrate [3] High GI, high carbohydrate	[1] NR [2] 20-25 [3] 20-25	[1] 39 [2] 52 [3] 47 12 months	[1] P: 19; F: total fat intake increased by ~10%; 40*; SFA: 10*; PUFA: 8*; MUFA: 18* [2] P: 21; F: 27* SFA: 8*; PUFA: 5*; MUFA: 11* [3] P: 20; F: 31* SFA: 10*; PUFA: 6*; MUFA: 12*	F, of which the majority MUFA	[1] 54; 44 (81%) [2] 56; 45 (80%) [3] 52; 41 (79%) 12 months *Retention rates at 3 and 6 months follow-up not reported.*	ITT	SA: H

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Wycherley, 2010[42] 4 months SA: HbA1c; 2% Body weight; 4%	[1] High protein [2] Energy restricted standard carbohydrate ISOCALORIC	[1] 43 [2] 53	[1] 47 [2] 54 7 4 months	[1] P: 33; F: 22; SFA: 6*; PUFA: 4*; MUFA: 8* [2 P: 19; F: 26; SFA: 8*; PUFA: 4*; MUFA: 10*	P&F, of which the majority SFA and MUFA	[1] 21; 12 (57%) [2] 19; 16 (84%) 4 months	PP	SA: U

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HbA1c: glycated haemoglobin; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low-density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number: NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10].

[a] In the MA of Sainsbury et al.[5], (very) low carbohydrate diet RCTs together contributed 26% weight to the full MA of HbA1c, and moderate carbohydrate diet RCTs together contributed 74% weight to the full MA of HbA1c, at both 3 and 6 months; In the MA of Sainsbury et al.[5], (very) low carbohydrate diet RCTs together contributed 33% weight to the full MA of body weight, and moderate carbohydrate diet RCTs together contributed 68% weight to the full MA of body weight at both 3 and 6 months; In the MA of McArdle et al.[11], low carbohydrate diet RCTs together contributed 17% to the full MA of HbA1c and 19% to the full MA of weight;

[b] Values are energy % unless indicated otherwise;

[c] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available.

D long-term RCTs on HbA1c and body weight

Table A3 Individual RCTs included in the evaluation of long-term effects of reduced carbohydrate diets on HbA1c and body weight: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Saslow, 2017[14] 12 months Individual RCT HbA1c Body weight	[1] very low carbohydrate, ketogenic, high fat, non-calorie restricted [2] moderate carbohydrate, calorie restricted, low fat	[1] 20-50 g [2] 45-50; 165 g	[1] 74 g [2] 150 g 12 months	[1] P: 98 g* ; F: 105 g* [2] P: 69 g* ; F: 75 g*	P&F	[1] 16; 14 (87%) [2] 18; 15 (83%) 12 months	NR	L
Stern, 2004[44] 12 months SA: HbA1c; 3%	[1] Low carbohydrate [2] Conventional	[1] < 30 g [2] NR	[1] 33; 120 g [2] 51; 230 g 12 months	[1] P: 73 g*; F: 93 g*; SFA: 19 g* [2] P: 74 g*; F: < 30 g; SFA: 17 g*	F, of which the majority UFA	[1] 27; 18 (67%) [2] 27; 16 (59%) 12 months	ITT	SA: L
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Davis, 2009[28] 12 months SA: HbA1c; 6% Body weight; 6%	[1] Low carbohydrate [2] Low fat	[1] 2 week phase of 20-25g, followed by a weekly increase of 5 g [2] NR	[1] 33 [2] 50 12 months	[1] P: 23*; F: 44*; SFA: 29*; PUFA: 18*; MUFA: 41* [2] P: 19*; F: 25; SFA: 30*; PUFA: 21*; MUFA: 38*	P&F, of which the majority MUFA & PUFA	[1] 55; 47 (85%) [2] 50; 44 (88%) 12 months	ITT	SA: U
Guldbrand, 2012[45] 12 months SA: HbA1c; 1% Body weight; 3%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	[1] 31 [2] 47 24 months	[1] P: 30; F: 50; SFA: 19; PUFA: 6; MUFA: 16 [2] P: 10-15; F: 30; SFA < 10; PUFA: 5*; MUFA: 11	P&F, of which majority SFA and MUFA	[1] 30; 26 (87%) [2] 31; 28 (90%) 24 months	ITT	SA: L
Sato, 2017[16] 18 months Individual RCT HbA1c Body weight	[1] Low carbohydrate [2] Calorie restricted	[1] 130 g [2] 50-60	[1] 214 g [2] 215 g 18 months	[1] P; 72 g*; F: 55 g*; SFA: 15g*; PUFA: 10g* MUFA: 20g* [2] P: 68 g*; F: 52 g*; SFA: 14g*; PUFA: 11g*; MUFA: 19g*	None	[1] 33; 27 (82%) [2] 33; 22 (67%) 18 months	NR	H

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Tay, 2015[43] 12 months SA: HbA1c; 9% Body weight; 4%	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 16 [2] 49 12 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 41 (71%) [2] 57; 37 (65%) 12 months	PP	SA: L
Tay, 2018[15] 24 months Individual RCT HbA1c Body weight	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 19 [2] 48 24 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 33 (57%) [2] 57; 28 (49%) 24 months	ITT	L
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Brehm, 2009[38] 12 months SA: HbA1c; 4% Body weight; 7%	[1] High MUFA [2] High carbohydrate ISOCALORIC	[1] 45 [2] 60	[1] 46 [2] 54 12 months	[1] P: 15; F: 40; MUFA: 20 [2] P: 15; F: 25; MUFA: 9*	F; of which majority likely MUFA	[1] 62; 43 (69%) [2] 62; 52 (85%) 12 months	PP	SA: U
Brinkworth, 2004[47] 12 months SA: HbA1c; 3% Body weight; 3%	[1] high protein [2] low protein ISOCALORIC	[1] 40 [2] 55	[1] NR [2] NR	[1] P: 30; F: 30; SFA: 8; PUFA: 5; MUFA: 12 [2] P: 15; F: 30; SFA: 8; PUFA: 5; MUFA: 12	P	[1] 33; 19 (56%) [2] 31; 19 (61%) 16 months	PP	SA: H
Elhayany, 2010[46] 12 months SA: HbA1c; 10% Body weight; 21%	[1] Low carbohydrate Mediterranean [2] Traditional Mediterranean [3] American Diabetes Association 2003 ISOCALORIC	[1] 35 [2] 50 [3] 50	[1] 42 [2] 45 [3] 45 6 months	[1] P: 20; F: 45; SFA: 7; PUFA: 15; MUFA: 23 [2] P: 20; F: 30; SFA: 7; PUFA: 12; MUFA: 10 [3] P: 20; F: 30; SFA: 7; PUFA: 12; MUFA: 10	F, of which majority MUFA	[1] 85; 61 (72%) [2] 89; 63 (71%) [3] 85; 55 (65%) 12 months	PP	SA: U
Fabricatore, 2011[40] 9 months SA: Body weight; 4%	[1] Low GL [2] Low fat ISOCALORIC	[1] NR [2] NR	[1] 41 [2] 50 9 months	[1] P: 20*; F: 40-60 g, dependent on kcal intake [2] P: 19*; F: ≤ 30 No subtypes reported.	F	[1] 40; 24 (60%) [2] 39; 26 (67%) 9 months	ITT	SA: L

First author, year; duration; MA: health outcome: % weight in MA [a]	Intervention groups	Prescribed CHO intake[b]	Achieved[b,c] CHO intake; month of assessment	Prescribed[b,c] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Krebs, 2012[34] 12 months SA: HbA1c; 18% Body weight; 11%	[1] Low fat higher protein [2] Low fat higher carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 46 [2] 48 24 months	[1] P: 30; F: 30; SFA: 13* [2] P: 15: F: 30; SFA: 12*	P	[1] 207; 144 (70%) [2] 212; 150 (71%) 24 months	ITT	SA: L
Larsen, 2011[35] 12 months SA: HbA1c; 14% Body weight; 21%	[1] High protein [2] High carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 42 [2] 48 12 months	[1] P: 30 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13 [2] P: 15 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13	P	[1] 53; 43 (81%) [2] 46; 37 (80%) 12 months	ITT	SA: L
Pedersen, 2014[48] 12 months SA: HbA1c; 5% Body weight; 3%	[1] High protein to carbohydrate ratio [2]Standard protein diet ISOCALORIC	[1] 40 [2] 50	[1] 40 [2] 45 12 months	[1] P: 30; F: 30; SFA: 30g*; PUFA 12g*; MUFA: 28g* [2] P: 20; F: 30; SFA: 23g*; PUFA 12g*; MUFA: 22g*	P	[1] 28; 21 (75%) [2] 38; 24 (63%) 12 months	ITT	SA: U
Wolever, 2008[26] 12 months SA: HbA1c; 24% Body weight; 22%	[1] Low carbohydrate, high MUFA [2] Low GI, high carbohydrate [3] High GI, high carbohydrate	[1] NR [2] 20-25 [3] 20-25	[1] 39 [2] 52 [3] 47 12 months	[1] P: 19; F: total fat intake increased by ~10%; 40*; SFA: 10*; PUFA: 8*; MUFA: 18* [2] P: 21; F: 27* SFA: 8*; PUFA: 5*; MUFA: 11* [3] P: 20; F: 31* SFA: 10*; PUFA: 6*; MUFA: 12*	F, of which the majority MUFA	[1] 54; 44 (81%) [2] 56; 45 (80%) [3] 52; 41 (79%) 12 months	ITT	SA: H

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HbA1c: glycated haemoglobin; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low-density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10].

[a] In the MA of Sainsbury et al.5, The (very) low carbohydrate diet RCTs together contributed 18% weight to the full MA of HbA1c, and moderate carbohydrate diet RCTs together contributed 82% weight to the full MA of HbA1c; The (very) low carbohydrate diet RCTs together contributed 13% weight to the full MA of weight, and moderate carbohydrate diet RCTs together contributed 87% weight to the full MA of weight;

[b] Values are energy % unless indicated otherwise;

[c] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available.

E short-term RCTs on fasting plasma glucose

Table A4 Individual RCTs included in the evaluation of short-term effects of reduced carbohydrate diets on fasting plasma glucose: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Goday, 2016[49] 4 months vZ: FPG: 19%	[1] Very low calorie ketogenic diet [2] Low calorie diet	[1] <50 g [2] 45-60	[1] NR [2] NR	[1] P: 0.8 to 1.2 g/ideal body weight; F: NR [2] P: 10-20; F: <30 Subtypes not reported.	Unclear	[1] 45; 40 (89%) [2] 44; 36 (82%) 4 months	ITT	vZ: U
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Shai, 2008[50] 6 months vZ: FPG: 24%	[1] Low carbohydrate, non-restricted calorie [2] Low fat, restricted calorie	[1] ≤ 120 g [2] NR	[1] 41 [2] 50 6 months; values are for whole study population, whereas subgroup analyses were used for estimates among people with T2D.	[1] P: 22*; F: 39* [2] P: 20*; F: ≤ 30; SFA: ≤ 10	P&F, specifically UFA	[1] 19; 12 (63%) [2] 12; 11 (92%) 24 months	ITT	vZ: U
Tay, 2014 [51] 6 months vZ: FPG: 11%	[1] Low carbohydrate, high unsaturated, low saturated fat [2] High carbohydrate, low fat ISOCALORIC	[1] 14 [2] 53	[1] 14 [2] 50	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 46 (79%) [2] 57; 47 (82%) 6 months	PP	vZ: U
Yamada, 2014[52] 6 months vZ FPG: 7%	[1] Low carbohydrate [2] Conventional calorie-restricted	[1] 70-130 g [2] 50-60	[1] 30; 126 g [2] 51; 203 g 6 months	[1] P: 25*; F: 45* [2] P: <20 F: <25 Subtypes not reported.	P&F	[1] 12; 12 (100%) [2] 12; 12 (100%) 6 months	PP	vZ: U

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
De Bont, 1981[53] 6 months vZ: FPG: 29%	[1] low carbohydrate [2] low fat	[1] 40 [2] NR	[1] 38 [2] 46 6 months	[1] P: 20*; F: 42*; SFA: 20*; PUFA: 5*; MUFA: 17* [2] P: 20*; F: 30; SFA: 12*; PUFA: 8*; MUFA: 11*	F, of which the majority SFA and MUFA	[1] NR; 65 (NR) [2] NR; 71 (NR) [1+2] 148; 136 (92%) 6 months	PP	vZ: U
Liu, 2018[12] 3 months Individual RCT FPG	[1] Low carbohydrate [2] High carbohydrate, low protein, low omega-3 PUFA ISOCALORIC	[1] 42 [2] 54	[1] NR [2] NR 3 months	[1] P: 28 ; F: 30 [2] P: 17 ; F: 29 Subtypes not reported.	P	[1] 30; 26 (87%) [2] 30; 25 (83%) 3 months	ITT	L
Wang, 2018[13] 3 months Individual RCT FPG	[1] Low carbohydrate [2] Low fat diet	[1] < 45 [2] NR	[1] 39 [2] 56 3 months	[1] P: 19*; F: 42* [2] P: 18*; F: 26* Subtypes not reported.	F	[1] 28; 24 (86%) [2] 28; 25 (89%) 3 months	ITT	Some concerns

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low-density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10].

[a] Values are energy % unless indicated otherwise;

[b] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available.

F long-term RCTs on fasting plasma glucose

Table A5 Individual RCTs included in the evaluation of long-term effects of reduced carbohydrate diets on fasting plasma glucose: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Shai, 2008[50] 12 months vZ: FPG: 27%	[1] Low carbohydrate, non-restricted calorie [2] Low fat, restricted calorie	[1] 120 g [2] NR	[1] 42 [2] 51 12 months; values are for whole study population, whereas subgroup analyses were used for estimates among people with T2D.	[1] P: 22*; F: 39* [2] P: 20*; F: ≤ 30; SFA: ≤ 10	P&F, specifically UFA	[1] 19; 12 (63%) [2] 12; 11 (92%) 24 months	ITT	vZ: U
Tay, 2018[15] 24 months Individual RCT FPG	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 19 [2] 48 24 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 33 (57%) [2] 57; 28 (49%) 24 months	ITT	L
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Elhayany, 2010[46] 12 months vZ: FPG: 27%	[1] Low carbohydrate Mediterranean [2] American Diabetes Association 2003 ISOCALORIC	[1] 35 [2] 50	[1] 42 [3] 45 6 months	[1] P: 20; F: 45; SFA: 7; PUFA: 15; MUFA: 23 [2] P: 20; F: 30; SFA: 7; PUFA: 12; MUFA: 10	F, of which majority MUFA	[1] 85; 61 (72%) [2] 85; 55 (65%) 12 months	PP	vZ: H
Hockaday, 1978[54] 12 months vZ: FPG: 19%	[1] Low carbohydrate [2] High carbohydrate, modified fat ISOCALORIC	[1] 40 [2] 54	[1] NR [2] NR	[1] P: 20; F: 40; SFA: 28; PUFA: 12 [2] P: 20; F: 26; SFA: 10; PUFA: 16	F, specifically SFA	[1] 54; 54 (100%) [2] 39; 39 (100%) 12 months	ITT	vZ: U

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Wolever, 2008[26] 12 months vZ: FPG: 28%	[1] Low carbohydrate, high MUFA [2] Low GI, high carbohydrate [3] High GI, high carbohydrate	[1] NR [2] 20-25 [3] 20-25	[1] 39 [2] 52 [3] 47 12 months	[1] P: 19; F: total fat intake increased by ~10%; 40*; SFA: 10*; PUFA: 8*; MUFA: 18* [2] P: 21; F: 27* SFA: 8*; PUFA: 5*; MUFA: 11* [3] P: 20; F: 31* SFA: 10*; PUFA: 6*; MUFA: 12*	F, of which the majority MUFA	[1] 54; 44 (81%) [2] 56; 45 (80%) [3] 52; 41 (79%) 12 months	ITT	vZ: U

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low-density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10]

[a] Values are energy % unless indicated otherwise;

[b] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available;

G short-term RCTs on LDL cholesterol

Table A6 Individual RCTs included in the evaluation of short-term effects of reduced carbohydrate diets on LDL cholesterol: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Goday, 2016[49] 4 months vZ: LDLC: 17%	[1] Very low calorie ketogenic diet [2] Low calorie diet	[1] <50 g [2] 45-60	[1] NR [2] NR	[1] P: 0.8 to 1.2 g/ideal BW; F: NR [2] P: 10-20; F: <30 Subtypes not reported.	Unclear	[1] 45; 40 (89%) [2] 44; 36 (82%) 4 months	ITT	vZ: U
Westman, 2008[31] 6 months KH: LDLC: 4%	[1] Low carbohydrate, ketogenic [2] Low GI, reduced calorie	[1] <20 g [2] 55	[1] 13; 49 g [2] 44; 149 g 6 months	[1] P: 28* F: 59* [2] P: 20* F: 36* Subtypes not reported.	P&F	[1] 38; 21 (55%) [2] 46; 29 (63%) 6 months	PP	KH: H
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Davis, 2009[28] 6 months vZ: LDLC: 30%	[1] Low carbohydrate [2] Low fat	[1] 2 week phase of 20-25g, followed by a weekly increase of 5 g [2] NR	[1] 34 [2] 48 6 months	[1] P: 23*; F: 44*; SFA: 29*; PUFA: 18*; MUFA: 41* [2] P: 19*; F: 25; SFA: 30*; PUFA: 21*; MUFA: 38*	P&F, of which the majority MUFA & PUFA	[1] 55; 47 (85%) [2] 50; 44 (88%) 12 months	ITT	vZ: U
Guldbrand, 2012[45] 6 months vZ: LDLC: 20% ISOCALORIC	[1] Low carbohydrate [2] Low fat	[1] 20 [2] 55-60	[1] 25 [2] 49 6 months	[1] P: 30; F: 50; SFA: 19; PUFA: 6; MUFA: 16 [2] P: 10-15; F: 30; SFA < 10; PUFA: 5*; MUFA: 11	P&F, of which majority SFA and MUFA	[1] 30; 26 (87%) [2] 31; 28 (90%) 24 months	ITT	vZ: U
Jonasson, 2014[29] 6 months KH: LDLC: 5%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	[1] 25 [2] 49 6 months	[1] P: 23*; F: 49; SFA: 20*; PUFA: 8*; MUFA: 18* [2] P: 20*; F: 30; SFA 11*; PUFA: 5*; MUFA: 11*	P&F, of which majority SFA and MUFA	[1] 30; 30 (100%) [2] 31; 31 (100%) 6 months	NR	KH: H

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Tay, 2014[51] 6 months vZ: LDLC: 21%	[1] Low carbohydrate, high unsaturated, low saturated fat [2] High carbohydrate, low fat ISOCALORIC	[1] 14 [2] 53	[1] 14 [2] 50	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 46 (79%) [2] 57; 47 (82%) 6 months	PP	vZ: U
Yamada, 2014[52] 6 months vZ LDLC: 13% KH: LDLC: 5%	[1] Low carbohydrate [2] Conventional calorie-restricted	[1] 70-130 g [2] 50-60	[1] 30; 126 g [2] 51; 203 g 6 months	[1] P: 25*; F: 45* [2] P: <20 F: <25 Subtypes not reported.	P&F	[1] 12; 12 (100%) [2] 12; 12 (100%) 6 months	PP	vZ: U KH: H
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Jenkins, 2014[56] 3 months KH: LDLC: 13%	[1] Low GL with α-linolenic acid and MUFA [2] Wholegrain diet	[1] NR [2] NR	[1] 39 [2] 49	[1] P: 20*; F: 37*; SFA: 8*; PUFA: 9*; MUFA: 17* [2] P: 20*: F: 27*; SFA: 8*; PUFA: 7*; MUFA: 10*	F, of which majority MUFA	[1] 70; 55 (79%) [2] 71; 64 (90%) 3 months	ITT	KH: L
Liu, 2018[12] 3 months Individual RCT LDLC	[1] Low carbohydrate [2] High carbohydrate, low protein, low omega-3 PUFA ISOCALORIC	[1] 42 [2] 54	[1] NR [2] NR 3 months	[1] P: 28 ; F: 30 [2] P: 17 ; F: 29 Subtypes not reported.	P	[1] 30; 26 (87%) [2] 30; 25 (83%) 3 months	ITT	L
Luger, 2013[36] 3 months KH: LDLC: 4%	[1] High protein [2] The European Association for Diabetes recommendations ISOCALORIC	[1] 40 [2] 55	[1] 38 [2] 50 3 months	[1] P: 30 ; F: 30 [2] P: 15 ; F: 30 Subtypes not reported.	P	[1] 22; 20 (91%) [2] 22; 22 (100%) 3 months	PP	KH: H
McLaughlin, 2007[55] 4 months KH: LDLC: 3%	[1] 40% carbohydrate [2] 60% carbohydrate ISOCALORIC	[1] 40 [2] 60	[1] 43 [2] 52	[1] P: 15; F: 45; SFA: < 7 [2] P: 15; F: 25; SFA < 7	F, specifically UFA	[1] 14; 14 (100%) [2] 15; 15 (100%) 4 months	NR	KH: U

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ, van Zuuren et al.[10].

[a] Values are energy % unless indicated otherwise;

[b] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available;

H long-term RCTs on LDL cholesterol

Table A7 Individual RCTs included in the evaluation of long-term effects of reduced carbohydrate diets on LDL cholesterol: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Mayer, 2014[58] 11 months HU: LDLC: 12%	[1] Low carbohydrate [2] Low fat and orlistat	[1] ≤20 g [2] NR	[1] 18 [2] 44 11 months	[1] P: NR; F: 55 g [2] P: NR; F: <30; SFA <10	Unclear	[1] 22; NR [2] 24; NR	ITT	HU: NR
Saslow, 2017[14] 12 months Individual RCT LDLC	[1] very low carbohydrate, ketogenic, high fat, non-calorie restricted [2] moderate carbohydrate, calorie restricted, low fat	[1] 20-50 g [2] 45-50; 165 g	[1] 74 g [2] 150 g 12 months	[1] P: 98 g* ; F: 105 g* [2] P: 69 g* ; F: 75 g* Subtypes not reported.	P&F	[1] 16; 14 (87%) [2] 18; 15 (83%) 12 months	NR	L
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Davis, 2009[28] 12 months HU: LDLC: 36% KH: LDLC: 8%	[1] Low carbohydrate [2] Low fat	[1] 2 week phase of 20-25g, followed by a weekly increase of 5 g [2] NR	[1] 33 [2] 50 12 months	[1] P: 23*; F: 44*; SFA: 29*; PUFA: 18*; MUFA: 41* [2] P: 19*; F: 25; SFA: 30*; PUFA: 21*; MUFA: 38*	P&F, of which the majority MUFA & PUFA	[1] 55; 47 (85%) [2] 50; 44 (88%) 12 months	ITT	HU: NR KH: U
Guldbrand, 2012[45] 12 months HU: LDLC: 16%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	12 months: [1] 27 [2] 47 24 months: [1] 31 [2] 47	[1] P: 30; F: 50; SFA: 19; PUFA: 6; MUFA: 16 [2] P: 10-15; F: 30; SFA < 10; PUFA: 5*; MUFA: 11	P&F, of which majority SFA and MUFA	[1] 30; 26 (87%) [2] 31; 28 (90%) 24 months	ITT	HU: NR

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Sato, 2017[16] 18 months Individual RCT LDLC	[1] Low carbohydrate [2] Calorie restricted	[1] 130 g [2] 50-60	[1] 214 g [2] 215 g 18 months	[1] P; 72 g*; F: 55 g*; SFA: 15g*; PUFA: 10g* MUFA: 20g* [2] P: 68 g*; F: 52 g*; SFA: 14g*; PUFA: 11g*; MUFA: 19g*; (1.0 to 1.2 g/kg protein, and the remainder as fat)	None	[1] 33; 27 (82%) [2] 33; 22 (67%) 18 months	NR	S
Tay, 2015[43] 12 months HU: LDLC: 7%	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 16 [2] 49 12 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 41 (71%) [2] 57; 37 (65%) 12 months	PP	HU: NR
Tay, 2018[15] 24 months Individual RCT LDLC	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 19 [2] 48 24 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 33 (57%) [2] 57; 28 (49%) 24 months	ITT	L
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Brinkworth, 2004[47] 16 months KH: LDLC: 3%	[1] high protein [2] low protein ISOCALORIC	[1] 40 [2] 55	[1] NR [2] NR	[1] P: 30; F: 30; SFA: 8; PUFA: 5; MUFA: 12 [2] P: 15; F: 30; SFA: 8; PUFA: 5; MUFA: 12	P	[1] 33; 19 (56%) [2] 31; 19 (61%) 16 months	PP	KH: L
Elhayany, 2010[46] 12 months KH: LDLC: 9%	[1] Low carbohydrate Mediterranean [2] Traditional Mediterranean [3] American Diabetes Association 2003 ISOCALORIC	[1] 35 [2] 50 [3] 50	[1] 42 [2] 45 [3] 45 6 months (no 12 months available)	[1] P: 20; F: 45; SFA: 7; PUFA: 15; MUFA: 23 [2] P: 20; F: 30; SFA: 7; PUFA: 12; MUFA: 10 [3] P: 20; F: 30; SFA: 7; PUFA: 12; MUFA: 10	F, of which majority MUFA	[1] 85; 61 (72%) [2] 89; 63 (71%) [3] 85; 55 (65%) 12 months	PP	KH: H
Facchini, 2003[59] Mean 47 months (SD 22) KH: LDLC: 3%	[1] Carbohydrate-restricted [2] Standard protein restriction	[1] 35 [2] 65	[1] NR [2] NR	[1] P: 25-30: F: 30 [2] P: 10; F: 25 Subtypes not reported	P&F	[1] 100; 91 (91%) [2] 91; 79 (87%) 47 months	ITT	KH: H

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Krebs, 2012[34] 24 months KH: LDLC: 10%	[1] Low fat higher protein [2] Low fat higher carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 46 [2] 48 24 months	[1] P: 30; F: 30; SFA: 13* [2] P: 15: F: 30; SFA: 12*	P	[1] 207; 144 (70%) [2] 212; 150 (71%) 24 months	ITT	KH: L
Larsen, 2011[35] 12 months KH: LDLC: 8% HU: LDLC: 28%	[1] High protein [2] High carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 42 [2] 48 12 months	[1] P: 30 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13 [2] P: 15 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13	P	[1] 53; 43 (81%) [2] 46; 37 (80%) 12 months	ITT	KH: L HU: NR
Pedersen, 2014[48] 12 months KH: LDLC: 8%	[1] High protein to carbohydrate ratio [2]Standard protein diet ISOCALORIC	[1] 40 [2] 50	[1] 40 [2] 45 12 months	[1] P: 30; F: 30; SFA: 30g*; PUFA 12g*; MUFA: 28g* [2] P: 20; F: 30; SFA: 23g*; PUFA 12g*; MUFA: 22g*	P	[1] 28; 21 (75%) [2] 38; 24 (63%) 12 months	ITT	KH: L
Wolever, 2008[26] 12 months KH: LDLC: 12%	[1] Low carbohydrate, high MUFA [2] Low GI, high carbohydrate [3] High GI, high carbohydrate	[1] NR [2] 20-25 [3] 20-25	[1] 39 [2] 52 [3] 47 12 months	[1] P: 19; F: total fat intake increased by ~10%; 40*; SFA: 10*; PUFA: 8*; MUFA: 18* [2] P: 21; F: 27* SFA: 8*; PUFA: 5*; MUFA: 11* [3] P: 20; F: 31* SFA: 10*; PUFA: 6*; MUFA: 12*	F, of which the majority MUFA	[1] 54; 44 (81%) [2] 56; 45 (80%) [3] 52; 41 (79%) 12 months	ITT	KH: U

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10].

[a] Values are energy % unless indicated otherwise;

[b] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available.

I short-term RCTs on systolic blood pressure

Table A8 Individual RCTs included in the evaluation of short-term effects of reduced carbohydrate diets on systolic blood pressure: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Westman, 2008[31] 6 months KH: SBP: 2%	[1] Low carbohydrate, ketogenic [2] Low GI, reduced calorie	[1] <20 g [2] 55	[1] 13; 49 g [2] 44; 149 g 6 months	[1] P: 28* F: 59* [2] P: 20* F: 36* Subtypes not reported.	P&F	[1] 38; 21 (55%) [2] 46; 29 (63%) 6 months	PP	KH: H
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Daly, 2006[27] 3 months KH: SBP: 3%	[1] Low carbohydrate [2] Low fat	[1] ≤ 70 g [2] NR	[1] 34; 110 g [2] 45; 169 g 3 months	[1] P: 26*; F: 40*; SFA: 14* [2] P: 21*; F: 33*; SFA: 11*	P&F, of which the majority UFA	[1] 51; 40 (78%) [2] 51; 39 (76%)	PP	KH: U
Davis, 2009[28] 6 months vZ: SBP: 14%	[1] Low carbohydrate [2] Low fat	[1] 2 week phase of 20-25g, followed by a weekly increase of 5 g [2] NR	[1] 34 [2] 48 6 months	[1] P: 23*; F: 44*; SFA: 29*; PUFA: 18*; MUFA: 41* [2] P: 19*; F: 25; SFA: 30*; PUFA: 21*; MUFA: 38*	P&F, of which the majority MUFA & PUFA	[1] 55; 47 (85%) [2] 50; 44 (88%) 12 months	ITT	vZ: U
Guldbrand, 2012[45] 6 months vZ: SBP: 33%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	[1] 25 [2] 49 6 months	[1] P: 30; F: 50; SFA: 19; PUFA: 6; MUFA: 16 [2] P: 10-15; F: 30; SFA <10; PUFA: 5*; MUFA: 11	P&F, of which majority SFA and MUFA	[1] 30; 26 (87%) [2] 31; 28 (90%) 24 months	ITT	vZ: U
Tay, 2014[51] 6 months vZ: SBP: 32%	[1] Low carbohydrate, high unsaturated, low saturated fat [2] High carbohydrate, low fat ISOCALORIC	[1] 14 [2] 53	[1] 14 [2] 50	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 46 (79%) [2] 57; 47 (82%) 6 months	PP	vZ: U
Yamada, 2014[52] 6 months KH: SBP: 2% vZ: SBP: 22%	[1] Low carbohydrate [2] Conventional calorie-restricted	[1] 70-130 g [2] 50-60	[1] 30; 126 g [2] 51; 203 g 6 months	[1] P: 25*; F: 45* [2] P: <20; F: <25 Subtypes not reported.	P&F	[1] 12; 12 (100%) [2] 12; 12 (100%) 6 months	PP	vZ: U KH: H

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Jenkins, 2014[56] 3 months KH: SBP: 32%	[1] Low GL with α-linolenic acid and MUFA [2] Wholegrain diet	[1] NR [2] NR	[1] 39 [2] 49	[1] P: 20*; F: 37*; SFA: 8*; PUFA: 9*; MUFA: 17* [2] P: 20*: F: 27*; SFA: 8*; PUFA: 7*; MUFA: 10*	F, of which majority MUFA	[1] 70; 55 (79%) [2] 71; 64 (90%) 3 months	ITT	KH: L
Liu, 2018[12] 3 months Individual RCT SBP	[1] Low carbohydrate [2] High carbohydrate, low protein, low omega-3 PUFA ISOCALORIC	[1] 42 [2] 54	[1] NR [2] NR 3 months	[1] P: 28 ; F: 30 [2] P: 17 ; F: 29 Subtypes not reported.	P	[1] 30; 26 (87%) [2] 30; 25 (83%) 3 months	ITT	L
Luger, 2013[36] 3 months KH: SBP: 2%	[1] High protein [2] The European Association for Diabetes recommendations ISOCALORIC	[1] 40 [2] 55	[1] 38 [2] 50 3 months	[1] P: 30 ; F: 30 [2] P: 15 ; F: 30 Subtypes not reported.	P	[1] 22; 20 (91%) [2] 22; 22 (100%) 3 months	PP	KH: U
McLaughlin, 2007[55] 4 months KH: SBP: 2%	[1] 40% carbohydrate [2] 60% carbohydrate ISOCALORIC	[1] 40 [2] 60	[1] 43 [2] 52 4 months	[1] P: 15; F: 45; SFA: <7 [2] P: 15; F: 25; SFA <7	Fat, specifically UFA	[1] 14; 14 (100%) [2] 15; 15 (100%)	NR	KH:U

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10].

[a] Values are energy % unless indicated otherwise;

[b] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available.

J long-term RCTs on systolic blood pressure

Table A9 Individual RCTs included in the evaluation of long-term effects of reduced carbohydrate diets on systolic blood pressure: prescribed and achieved intakes of carbohydrates, prescribed protein and fat intakes and substitutions, number of participants and completers, type of data analysis and overall of risk of bias assessments.

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Very low (20 to 50 g/d; ≤10 en% CHO)								
Goldstein, 2011[61] 12 months KH: SBP: 0.4% HU: SBP: 2%	[1] Modified Atkins diet [2] American Diabetes Association (2001) calorie-restricted diet	[1] 25-40 g [2] NR	[1] 20 [2] 43 12 months	[1] P: 102 g*; F: 111 g*; SFA 32 g*, MUFA 29 g* [2] P: 10-20; F: SFA 9-10; PUFA 8-10; MUFA 18-20	P&F	[1] 26; 14 (54%) [2] 26; 16 (62%) 12 months	ITT	KH: U HU: NR
Mayer, 2014[58] 11 months HU: SBP: 9%	[1] Low carbohydrate [2] Low fat and orlistat	[1] ≤20 g [2] NR	[1] 18 [2] 44 11 months	[1] P: NR; F: 55 g [2] P: NR; F: <30; SFA <10	Unclear	[1] 22; NR [2] 24; NR	ITT	HU: NR
Low (>50 to <130 g/d; >10 to <26 en% CHO)								
Davis, 2009[28] 12 months KH: SBP: 3% HU: SBP: 9%	[1] Low carbohydrate [2] Low fat	[1] 2 week phase of 20-25g, followed by a weekly increase of 5 g [2] NR	[1] 33 [2] 50 12 months	[1] P: 23*; F: 44*; SFA: 29*; PUFA: 18*; MUFA: 41* [2] P: 19*; F: 25; SFA: 30*; PUFA: 21*; MUFA: 38*	P&F, of which the majority MUFA & PUFA	[1] 55; 47 (85%) [2] 50; 44 (88%) 12 months	ITT	KH: U HU: NR
Guldbrand, 2012[45] 24 months KH: SBP: 4% HU: SBP: 9%	[1] Low carbohydrate [2] Low fat ISOCALORIC	[1] 20 [2] 55-60	12 months: [1] 27 [2] 47 24 months: [1] 31 [2] 47	[1] P: 30; F: 50; SFA: 19; PUFA: 6; MUFA: 16 [2] P: 10-15; F: 30; SFA <10; PUFA: 5*; MUFA: 11	P&F, of which majority SFA and MUFA	[1] 30; 26 (87%) [2] 31; 28 (90%) 24 months	ITT	KH: U HU: NR

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Tay, 2015[43] 12 months HU: SBP: 16%	[1] Low carbohydrate, high unsaturated fat, low saturated fat [2] High carbohydrate, low-fat ISOCALORIC	[1] 14 [2] 53	[1] 16 [2] 49 12 months	[1] P: 28 F: 58; SFA: <10; MUFA: 35; PUFA: 13 [2] P: 17 F: 30; SFA: <10; MUFA: 15; PUFA: 9	P&F, of which majority MUFA	[1] 58; 41 (71%) [2] 57; 37 (65%) 12 months	PP	HU: NR
Moderate (130 to 230 g/d; 26 to 45 en% CHO)								
Brinkworth, 2004[47] 16 months KH: SBP: 2%	[1] high protein [2] low protein ISOCALORIC	[1] 40 [2] 55	[1] NR [2] NR	[1] P: 30; F: 30; SFA: 8; PUFA: 5; MUFA: 12 [2] P: 15; F: 30; SFA: 8; PUFA: 5; MUFA: 12	P	[1] 33; 19 (56%) [2] 31; 19 (61%) 16 months	PP	KH: L
Esposito, 2009[60] 48 months HU: SBP: 38%	[1] Low carbohydrate Mediterranean [2] Low fat ISOCALORIC	[1] ≤ 50 [2] NR	[1] 44 [2] 52 48 months	[1] P: 18*; F: ≥30; SFA: 10* [2] P: 18*: F: ≤30; SFA: 9*	F, of which the majority UFA	[1] 108; 98 (91%) [2] 107; 97 (91%) 48 months	ITT	HU: NR
Krebs, 2012[34] 24 months KH: SBP: 7%	[1] High protein [2] High carbohydrate ISOCALORIC	[1] 40 [2] 55	[1] 42 [2] 48 12 months	[1] P: 30; F: 30; SFA: 13* [2] P: 15: F: 30; SFA: 12*	P	[1] 207; 144 (70%) [2] 212; 150 (71%) 24 months	ITT	KH: L
Larsen, 2011[35] 12 months KH: SBP: 8% HU: SBP: 17%	[1] High protein to carbohydrate ratio [2] Standard protein diet ISOCALORIC	[1] 40 [2] 50	[1] 40 [2] 45 12 months	[1] P: 30 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13 [2] P: 15 ; F: 30; SFA: 7; PUFA: 10; MUFA: 13	P	[1] 53; 43 (81%) [2] 46; 37 (80%) 12 months	ITT	KH: L HU: NR
Pedersen, 2014[48] 12 months KH: SBP: 3%	[1] High protein to carbohydrate ratio [2]Standard protein diet ISOCALORIC	[1] 40 [2] 50	[1] 40 [2] 45 12 months	[1] P: 30; F: 30; SFA: 30g*; PUFA 12g*; MUFA: 28g* [2] P: 20; F: 30; SFA: 23g*; PUFA 12g*; MUFA: 22g*	P	[1] 28; 21 (75%) [2] 38; 24 (63%) 12 months	ITT	KH: L

First author, year; duration; MA: health outcome: % weight in MA	Intervention groups	Prescribed CHO intake[a]	Achieved[a,b] CHO intake; month of assessment	Prescribed[a,b] protein and fat intakes	Substitution macronutrient	N Participants; N completers (%); month of assessment	ITT/ PP	Overall RoB
Wolever, 2008[26] 12 months KH: SBP: 30%	[1] Low carbohydrate, high MUFA [2] Low GI, high carbohydrate [3] High GI, high carbohydrate	[1] NR [2] 20-25 [3] 20-25	[1] 39 [2] 52 [3] 47 12 months	[1] P: 19; F: total fat intake increased by ~10%; 40*; SFA: 10*; PUFA: 8*; MUFA: 18* [2] P: 21; F: 27* SFA: 8*; PUFA: 5*; MUFA: 11* [3] P: 20; F: 31* SFA: 10*; PUFA: 6*; MUFA: 12*	F, of which the majority MUFA	[1] 54; 44 (81%) [2] 56; 45 (80%) [3] 52; 41 (79%) 12 months	ITT	KH: U

CHO: carbohydrate; F: total fat; GI: glycaemic index; FPG: fasting plasma glucose; GL: glycaemic load; H: high risk of bias; HU: Huntriss et al.[9]; ITT: intention to treat; KH: Korsmo-Haugen et al.[18]; L: low risk of bias; LDLC: low density lipoprotein cholesterol; MA: meta-analysis; McA: McArdle et al.[11]; MUFA: monounsaturated fat; N: number; NR: not reported; P: total protein; PP: per protocol; PUFA: polyunsaturated fat; RoB: risk of bias; SA: Sainsbury et al.[5]; SFA: saturated fat; SBP: systolic blood pressure; T2D: type 2 diabetes; U: unclear risk of bias; UFA: unsaturated fat; vZ: van Zuuren et al.[10].

[a] Values are energy % unless indicated otherwise;

[b] Achieved values are means or medians, dependent on what was reported in the RCT article;

* Based on achieved intakes since prescribed was not available.

K risk of bias assessments of the RCTs

Table A10 Risk of bias assessments performed by meta-analysis (MA) authors, of the RCTs included in MA that evaluated the scientific evidence regarding the effect of low and moderate carbohydrate diets on HbA1c, body weight, fasting plasma glucose, LDL cholesterol, and systolic blood pressure in people with type 2 diabetes.

First author, year	MA	Domain*								Explanation**	Funding sources
		A	B	C	D	E	F	G	Overall		
Very low carbohydrate											
Goday, 2016[49]	vZ	?	?	?	+	?	+	+	U	The domain “incomplete outcome data” was scored as ? since: Analysis of the safety and tolerability (safety population) variables was performed with an intention-to-treat analysis with baseline or last observation carried forward when the complete set of data for an individual was not available. Changes in body weight between groups were compared in the ‘efficacy population’, composed by those with at least one efficacy measurement available after randomisation. Comment: Moderate number (13/89 (14.6%); balanced) of losses to follow-up judged as an unclear risk of bias.	Funding by Pronokal Group. Funding body not involved in study design, data collection, analysis or interpretation.
Goldstein, 2011[61]	KH	?	?	+	?	+	+	+	U		None
	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	
Mayer, 2014[58]	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	NIH T32 grant. Funding for original study: Department of Veterans Affairs.
Samaha, 2003[32]	SA	+	?	-	+	+	+	+	L		Veterans Affairs Healthcare Network Competitive Pilot Project Grant.
Saslow, 2014[24]	SA	+	+	-	+	+	+	+	L		William K. Bowes, Jr. Foundation and the Mount Zion Health Fund. Funders not involved in design, analysis, or publication.

First author, year	MA	Domain* A	B	C	D	E	F	G	Overall	Explanation**	Funding sources
Stern, 2004[44]	SA	+	?	-	+	+	+	+	L		Veterans Affairs Healthcare Network Competitive Pilot Project Grant.
Westman, 2008[31]	SA	+	?	-	+	-	+	?	H	The domain “incomplete outcome data” scored as - since: Low retention rates, with difference between-groups (55% vs 63%). Last observation carried forward analysis were performed for HbA1c only. In addition, only a small sample of food diaries were analysed (15 total).	Robert C Atkins Foundation. Funders involvement in study not specified.
	KH	+	?	?	-	?	+	?	H	No explanation was given for the domain scored high risk of bias.	
Low carbohydrate											
Daly, 2006[27]	SA	+	?	-	+	+	+	+	L		Diabetes UK
	McA	+	+	+	?	+	+	-	NR	The individual domain “other bias” was scored as - since there was no description of pre-study dietary intake.	
	KH	+	+	?	-	?	+	+	U	No explanation was given for the domain scored high risk of bias.	
Davis, 2009[28]	SA	+	?	-	+	+	+	?	U		Robert C. Atkins Foundation and Diabetes Research and Training Center and a Clinical and Translational Science Award. Funder involvement in study not specified.
	vZ	+	+	?	+	+	+	+	U		
	KH	+	?	?	?	+	+	+	U		
	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	
Guldbrand, 2012[45]	SA	+	?	-	+	+	+	+	L		University Hospital of Linköping, Linköping University, County Council of Östergötland, and Diabetes Research Centre of Linköping University.
	vZ	+	+	?	?	+	+	+	U		
	KH	+	+	?	-	+	+	+	U	No further explanation was given for the domain scored high risk of bias.	

First author, year	MA	Domain* A	B	C	D	E	F	G	Overall	Explanation**	Funding sources
	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	
Jonasson, 2014[29]	McA	+	+	?	?	+	+	+	NR		Not reported
	KH	+	+	-	?	?	+	+	L		
Jonsson, 2009[33]	McA	+	+	?	?	+	+	-	NR	The individual domain “other bias” was scored as - since there was no description of pre-study dietary intake.	Crafoordska stiftelsen, Region Skåne and Lund University
Sato, 2017[30]	McA	+	?	?	?	+	+	+	NR		Mishima Kaiun Memorial Foundation
Shai, 2008[50]	vZ	+	?	?	+	?	+	+	U	The individual domain “incomplete outcome data” was scored as ? since: Dropouts: 50/322 (11.5%); 24/109 (22%) in low carbohydrate diet group, 10/104 (9.6%) in low fat diet group, 16/109 (14.5%) in Mediterranean diet group, numbers of dropouts not completely balanced. Intention-to-treat analysis.	Nuclear Research Center Negev, Atkins Research Foundation, and S Daniel Abraham International Center for Health and Nutrition, Ben Gurion University.
Tay, 2014[51]	vZ	+	+	?	+	?	?	+	U	The individual domain “incomplete outcome data” was scored as ? since: Dropouts: 22/115 (19.1%); 12/58 in very low carbohydrate diet group, 10/57 in low fat diet group. Per-protocol analysis The moderate dropout rate combined with a per-protocol analysis poses an unclear risk of bias.	National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.
Tay, 2015[43]	SA	+	+	-	+	+	+	+	L		National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.
	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	
Yamada, 2014[52]	SA	?	?	-	+	+	+	+	U		Not reported.
	McA	+	?	?	?	+	+	-	NR	The individual domain “other bias” was scored as - since there was no description of pre-study dietary intake.	
	vZ	+	?	?	?	+	+	+	U		

First author, year	MA	Domain* A	B	C	D	E	F	G	Overall	Explanation**	Funding sources
	KH	+	?	?	-	+	-	+	H	No further explanation was given for the domains scored high risk of bias.	
Moderate carbohydrate											
De Bont, 1981[53]	vZ	?	?	?	+	+	+	+	U		Not reported.
Brehm, 2009[38]	SA	?	?	-	+	+	+	+	U		American Diabetes Association, U.S Public Health Service Grant; Cincinnati Children's Hospital Medical Center Clinical Research Center.
Brinkworth, 2004[47]	SA	+	?	-	+	-	+	?	H	The individual domain "incomplete outcome data" was scored as -. Completers only analysis were performed at 3 and 12 months, and there was a poor retention rate (38/64). In addition, there was an imbalanced baseline body weight between groups at 12 months.	Meadow Lea Foods, Mascot, NSW, Australia. Funders involvement in study not specified.
	KH	+	?	?	?	+	+	+	L		
Brunerova, 2007[39]	SA	?	?	-	+	?	-	+	H	Of the individual domain, "selective reporting" was scored as - since participant's dietary intake was not reported, but methods state this information was collected.	VZ MSM 0021620814
Elhayany, 2010[46]	SA	?	?	-	+	+	+	+	U		Not reported
	vZ	-	+	?	?	-	?	?	H	Reasons for high risk of bias: 1. Quasi-randomised poses a high risk of bias. 2. Dropouts: 80/259 (30.9%), balanced amongst groups. Comment: The high total number of dropouts although balanced between the groups, represents, combined with a per-protocol analysis, a high risk of bias.	
	KH	?	?	?	?	+	-	+	H	No explanation was given for the domain scored high risk of bias.	
Esposito, 2009[60]	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	Second University of Naples.
Fabricatore, 2011[40]	SA	+	?	-	+	+	+	+	L		National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Research Resources.
Facchini, 2003[59]	KH	?	?	?	?	+	+	?	U		Not reported.

First author, year	MA	Domain* A	B	C	D	E	F	G	Overall	Explanation**	Funding sources
Hockaday, 1978[54]	vZ	?	?	?	+	+	+	?	U		British Diabetic Association and from the International Sugar Research Foundation Inc.
Jenkins, 2014[56]	KH	?	?	?	+	+	+	+	L		Canola Council of Canada, Agriculture and Agri-Food Canada, and Loblaw Companies Canada.
Krebs, 2012[34]	SA	+	+	-	+	+	+	+	L		Health Research Council of New Zealand.
	KH	+	+	?	+	+	+	+	L		
Larsen, 2011[35]	SA	+	+	-	+	+	+	+	L		Meat and Livestock Australia. Funding bodies not involved in study design, data collection, analysis or interpretation.
	KH	+	+	?	+	?	+	+	L		
	HU	NR	NR	NR	NR	NR	NR	NR	NR	General information: Risk of bias was high in the majority of included trials due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention.	
Luger, 2013[36]	SA	?	?	-	+	+	+	+	U		Not reported.
	KH	?	?	?	?	+	+	?	U		
McLaughlin, 2007[55]	KH	?	?	?	?	+	+	+	L		National Institutes of Health Grants.
Parker, 2002[37]	SA	+	?	-	+	-	+	?	H	The individual domain “incomplete outcome data” scored as - since: Completers only analysis at 3 and 12 months. Poor retention (38/64) at 12 months. Imbalanced baseline body weight between groups at 12 months.	Meadow Lea Foods. Funders involvement in study not specified.
Pedersen, 2014[48]	SA	?	+	-	+	+	+	?	U		Corresponding author co-authored the CSIRO Total Wellbeing Diet
	KH	+	+	?	+	+	+	+	L		
Watson, 2016[41]	SA	?	+	-	+	+	+	?	U		Pork Cooperative Research Centre; study foods donated by various companies. Funders involvement in study not specified.
Wolever, 2008[26]	SA	+	+	-	+	-	+	-	H	The individual domain “incomplete outcome data” was scored as - since data were reported for completers only: ‘data on those who dropped out because of treatment failure were retained in the model up to and including the point at which they were declared to have failed…’.	Canadian Institutes of Health Research; foods donated by various companies. The domain “other bias” scored as - since the first author is president and part-owner of GI Index Testing Inc.

First author, year	MA	Domain* A	B	C	D	E	F	G	Overall	Explanation**	Funding sources
	vZ	+	+	?	+	?	?	+	U	The individual domain “incomplete outcome data” was scored as ? since: Dropouts: 32/162 (19.8%) balanced between groups. But 156 were included in the analyses, 6 refused at follow up.	
	KH	+	+	?	?	+	+	?	U		
Wycherley, 2010[42]	SA	?	?	-	+	+	+	+	U		National Heart Foundation of Australia; Diabetes Australia Research Trust; Pork Cooperative Research Centre; Geroge Weston Foods donated foods.

HU: Huntriss et al.[9]; KH: Korsmo-Haugen et al.[18]; MA: meta-analysis; McA: McArdle et al.[11]; NR: not reported; SA: Sainsbury et al.[5]; UK: United Kingdom; vZ: van Zuuren et al.[10].

* Domains addressed: A, random sequence generation; B, allocation concealment; C, blinding of participants and personnel; D, blinding of outcome assessment; E, incomplete outcome data; F, selective reporting; G, other bias. Judgements include: +, low risk of bias; ?, unclear risk of bias; -, high risk of bias;

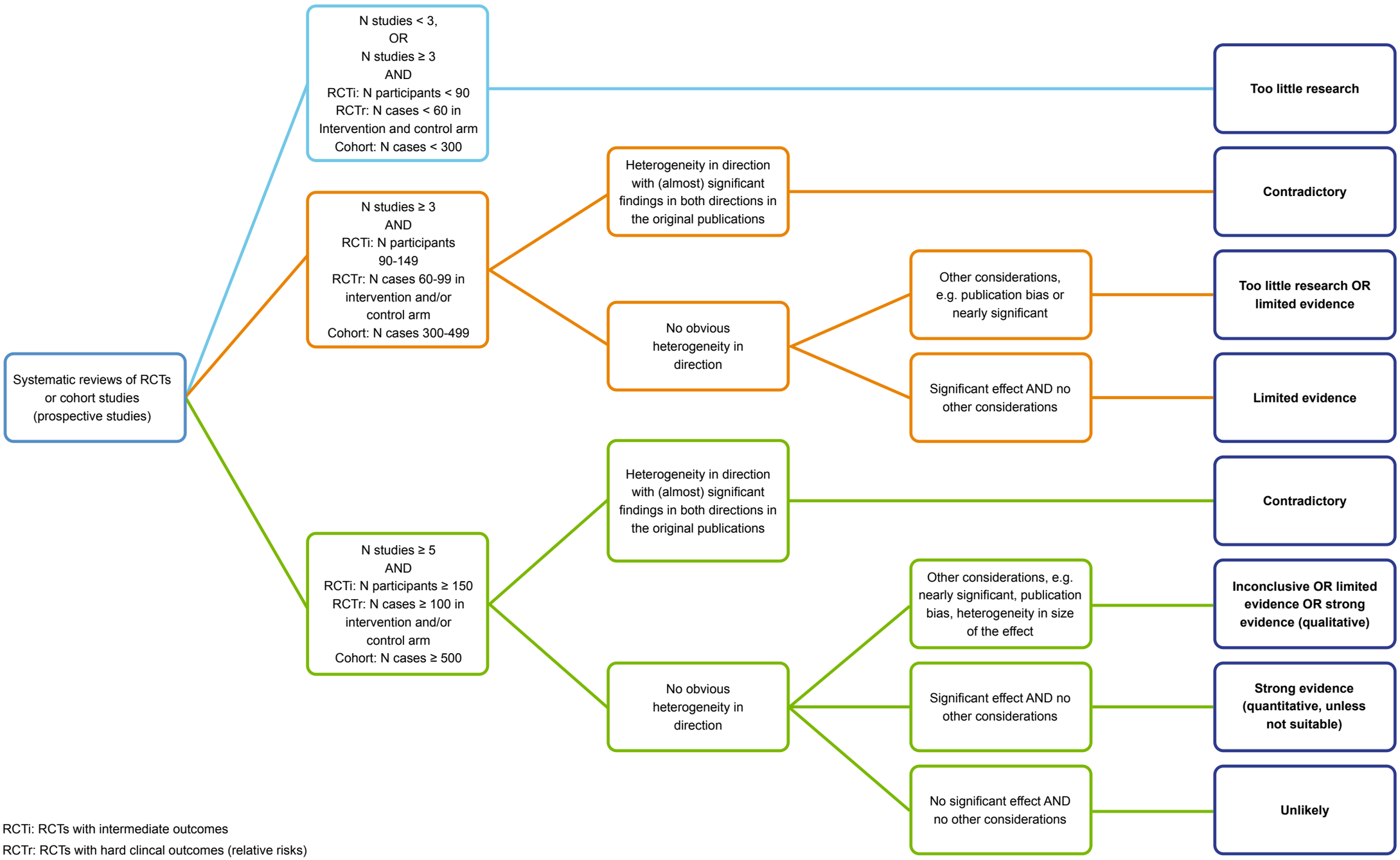
** No explanation is given when individual domain C (blinding of participants and personnel) is scored high since it is not feasible to blind participants and personnel in the type of studies under evaluation.

Table A11 Risk of bias assessments performed by the Committee, of the recent RCTs included in the evaluation of the scientific evidence regarding the effect of low and moderate carbohydrate diets on HbA1c, body weight, fasting plasma glucose, LDL cholesterol, and systolic blood pressure in people with type 2 diabetes.

First author, year	Domain* A	B	C	D	E	Overall	Explanation	Funding sources
Very low carbohydrate								
Saslow, 2017[14]	+	+	+	+	+	L		One of the authors was a paid member of the Atkins Scientific Advisory Board, a founder of Virta Health, and has authored books on low-carbohydrate, high fat diets. The research was supported by a grant from the William K. Bowes, Jr. Foundation and the Mount Zion Health Fund. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Low carbohydrate								
Sato, 2017 (2)[16]	+	+	x	+	x	S	There were moderate losses to follow-up (62/49), equal between groups. The missingness of data was (partly) related to health status of the participants.	Supported by Mishima Kaiun Memorial Foundation.
Struik, 2020[17]	+	+	+	+	+	L		Supported by a project grant received from National Health and Medical Research Council of Australia. The funding sponsors had no role in the design, data collection and analysis, the preparation of the manuscript, or decision to publish.
Tay, 2018[15]	+	+	+	+	+	L		Supported by a project grant received from National Health and Medical Research Council of Australia. The funding sponsors had no role in the design, data collection and analysis, the preparation of the manuscript, or decision to publish.
Moderate carbohydrate								
Liu, 2018[12]	+	+	+	+	+	L		Supported by the National Natural Science Foundation of China, Nutrition Science Foundation of BY-HEALTH, and Sansun Life Sciences Foundation. The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or decision to submit the manuscript for publication.
Wang, 2018[13]	x	+	+	+	+	S	Only baseline characteristics of participants included in the final analysis were presented.	Supported by Suzhou Science and Technology Project, China.

* Domains addressed: A, bias arising from the randomisation process; B, bias due to deviations from the intended interventions; C, bias due to missing outcome data; D, bias in measurement of the outcome; E, bias in selection of the reported result. Judgements include: +, low risk of bias; x, some concerns; -, high risk of bias; Overall risk of bias judgements include: L, low risk of bias; S, some concerns; H, high risk of bias.

L decision tree



RCTi: RCTs with intermediate outcomes

RCTr: RCTs with hard clincal outcomes (relative risks)

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
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