Lower carbohydrate diets for adults with type 2 diabetes

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Lower carbohydrate diets for adults with type 2 diabetes

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Summary

S.1 The purpose of this report was to review the evidence on ‘low’ carbohydrate diets compared to current UK government advice on carbohydrate intake for adults with type 2 diabetes (T2D).

S.2 It was initiated in response to a request from Public Health England, for a systematic assessment of the scientific evidence on ‘low’ carbohydrate diets, in recognition that such diets are increasingly being promoted.

S.3 Current UK government advice for the general UK population is that approximately 50% of total dietary energy (TE) should be obtained from carbohydrates. There are no separate recommendations on carbohydrate intake for adults with type 2 diabetes (T2D) and the advice for the general UK population also applies to those with T2D.

S.4 Since there is no agreed and widely used definition of a ‘low’ carbohydrate diet, comparisons in this report were between lower and higher carbohydrate diets.

Terms of reference

S.5 The terms of reference were to:

- review the evidence on lower carbohydrate diets (alongside higher fat and/or higher protein) compared to current government advice for adults with T2D
- consider the impact, in adults with T2D, of lower compared with higher carbohydrate diets on markers and clinical outcomes of T2D including any potential adverse effects
- make recommendations based on the review of the evidence.

Assessment of the evidence

S.6 This report is based on evidence from systematic reviews and meta-analyses of randomised controlled trials (RCTs) comparing effects of lower versus higher carbohydrate diets on markers and clinical outcomes of T2D.

S.7 Primary outcomes of interest were body weight (≥12 months) and glycated haemoglobin (HbA1c) (≥3 months). Secondary outcomes were: body weight (≥3 to <12 months); fasting plasma glucose (≥3 months); serum total cholesterol; serum triacylglycerol; serum low density lipoprotein (LDL) cholesterol; serum high density lipoprotein (HDL) cholesterol; serum total cholesterol:HDL cholesterol ratio) (≥3 months); and medication use. None of the systematic reviews with meta-analyses included in this review considered total cholesterol:HDL cholesterol ratio as an outcome.

S.8 In the evidence considered, outcomes were assessed in the shorter term (≥3 to ≤6 months) and in the longer term (≥12 months).

S.9 The evidence was graded as **adequate**, **moderate**, **limited**, **inconsistent** or **insufficient**. Only outcomes where the evidence base was graded as adequate or moderate were used to inform the recommendations.

S.10 Several limitations were identified in the evidence base and were considered in the assessment. These are summarised below:

- no agreed definition of a 'low' carbohydrate diet
- overlap in the reported mean carbohydrate intakes between lower (13 to 47% TE) and higher (41 to 55%) carbohydrate groups
- variation in the type and amount of macronutrient that replaced carbohydrate (fat and/or protein) and in the duration and intensity of advice given to participants on following their prescribed diets
- lack of detail on the types of carbohydrate consumed (for example, wholegrain, refined grain, free sugars, fibre) or consideration of how this could affect outcomes
- limited information on adherence to the prescribed intakes throughout the full duration of the study or consideration of how adherence might impact outcomes
- inconsistent assessment and reporting of medication use
- most shorter-term studies did not assess outcomes between 6 and 12 months and few longer-term studies assessed outcomes beyond 12 months
- risk of bias was assessed as high or unclear in most of the primary RCTs, reducing the confidence that can be placed on the estimates of the effects.

Evidence grading for all outcomes

S.11 Evidence grades for all the outcomes are summarised in Table S1.

Adverse events

S.12 The most common adverse events that were experienced included gastroenteritis, nausea, vomiting and headaches.

S.13 In the shorter term (≥3 to 6 months), there was no evidence of any difference in adverse events between lower and higher carbohydrate intakes in adults with T2D. The implications of longer-term (≥12 months) restriction of carbohydrates in adults with T2D are currently unknown due to a lack of data from longer-term intervention studies.

Conclusions

S.14 It was not possible to assess the impact of a ‘low’ compared to a ‘high’ carbohydrate diet on markers and clinical outcomes of T2D in adults with T2D because the definition of a low carbohydrate diet varied widely across the primary RCTs.

S.15 Prescribed carbohydrate intakes in lower carbohydrate groups ranged from 14 to 50% TE. There was also overlap in reported mean carbohydrate intakes between the lower (13 to 47% TE) and higher (41 to 55% TE) carbohydrate diets. Comparisons, therefore, were largely between lower and higher rather than ‘low’ and ‘high’ carbohydrate diets.

S.16 Overall, the evidence suggests beneficial effects of lower carbohydrate diets on HbA1c, fasting plasma glucose and serum triacylglycerol in the shorter term (up to 6 months).

S.17 Although there was no consistent evidence of reductions in body weight with lower carbohydrate diets, it is not possible from the evidence considered to separate the effects of weight change from effects of change in carbohydrate intake.

S.18 Lower carbohydrate diets may allow reductions in diabetes medication, but interpretation is complicated by inconsistencies in reporting and measurement of changes in medication use.

S.19 No differences were observed between higher and lower carbohydrate diets on serum total cholesterol or LDL cholesterol either in the shorter (≥3 to 6 months) or longer (≥12 months) term. Evidence on HDL cholesterol was inconsistent in the shorter (≥3 to 6 months) and longer (≥12 months) term.

S.20 In general, there was no difference in occurrence of adverse events between lower and higher carbohydrate diets in the shorter term (≥3 to 6 months) but the longer term (≥12 months) implications of lower carbohydrate diets are not known since study duration did not extend beyond 12 months in the majority of primary RCTs.

S.21 The overall quality of the evidence base was limited by a number of uncertainties and limitations in the data (see paragraph S.10 above).

S.22 It is not known if the reported effects of lower carbohydrate diets apply to individuals of different ethnicities since the majority of primary RCTs did not report ethnicity of participants and were conducted in populations that were predominantly White.

S.23 This report did not assess evidence on the effect of lower carbohydrate diets in the general population without T2D. It is not known if the reported effects of lower carbohydrate diets in adults with T2D apply to the general adult population without T2D.

S.24 The following gaps were identified in the evidence base and these informed the research recommendations (see chapter 8):

- effects of lower carbohydrate diets on individuals living with T2D from minority ethnic population groups was not considered
- no trials provided information about types of carbohydrate consumed (for example, wholegrain, refined grain, free sugars, fibre) or considered how this could affect the outcomes of interest
- the potential impact of increasing the proportions of other macronutrients (fats and/or proteins) to compensate for reduced carbohydrate intake in the lower carbohydrate groups, or the type of macronutrient (for example, saturated or unsaturated fats; plant or animal-based proteins), on markers and clinical outcomes of T2D was generally not considered
- few trials assessed adherence to dietary interventions throughout the study duration or considered how adherence might impact the outcomes
- few trials assessed longer-term effects (beyond 12 months) of lower carbohydrate diets
- no trials considered clinical endpoints such as diabetes complications, cardiovascular disease (CVD) events or mortality.

Recommendations

S.25 The recommendations are applicable to adults living with T2D and overweight or obesity. There was insufficient evidence to make recommendations for adults living with T2D without overweight or obesity. This report did not assess evidence on the effect of lower carbohydrate diets in the general population without T2D.

S.26 For adults living with T2D and overweight or obesity, a lower carbohydrate diet can be recommended by clinicians as an effective short-term option (up to 6 months) for improving glycaemic control and serum triacylglycerol concentrations.

S.27 Individuals living with T2D and overweight or obesity, who choose a lower carbohydrate diet, should include wholegrain or higher fibre foods, a variety of fruits and vegetables and limit intakes of saturated fats, reflecting current dietary advice for the general population.

S.28 Since the majority of individuals living with T2D have overweight or obesity, weight management remains the primary goal for improving glycaemic control and reducing CVD risk. Health professionals should support any evidence-based dietary approach that helps individuals with T2D to achieve long-term weight reduction.

S.29 Adults living with T2D and overweight or obesity who change to a lower carbohydrate diet and are taking diabetes medication may be at risk of

hypoglycaemia. It is recommended that they receive advice and support from their health care team to manage this risk and to make adjustments to their medication as required.

Table S1: Evidence grading for all outcomes

Outcome	Shorter term (≥3 to 6 months)	Longer term (≥12 months)
Body weight	**Inconsistent** evidence: greater reduction in body weight with lower compared to higher carbohydrate diets at 3 months; no difference between 3 and 6 months or at 6 months	**Adequate** evidence for no difference in effect between lower and higher carbohydrate diets in reducing body weight
HbA1c	**Adequate** evidence of a greater reduction in HbA1c with lower compared to higher carbohydrate diets	**Inconsistent** evidence at 12 up to 24 months. **Adequate** evidence for no difference between lower and higher carbohydrate diets on HbA1c change at 24 months
Fasting plasma glucose	**Moderate** evidence of a greater reduction in fasting plasma glucose with lower compared to higher carbohydrate diets	**Insufficient** evidence to assess if there was a difference between lower and higher carbohydrate diets on fasting plasma glucose
Serum total cholesterol	**Moderate** evidence for no difference in effect between lower and higher carbohydrate diets in reducing serum total cholesterol	**Adequate** evidence for no difference in effect between lower and higher carbohydrate diets in reducing serum total cholesterol
Serum triacylglycerol	**Adequate** evidence of a greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets	**Inconsistent** evidence
Serum LDL cholesterol	**Adequate** evidence for no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol	**Adequate** evidence for no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol
Serum HDL cholesterol	**Inconsistent** evidence	**Inconsistent** evidence
Medication use	**Moderate** evidence of a greater reduction in medication use with lower compared to higher carbohydrate diets (outcome not assessed by study duration)	

1 Introduction

1.1 The purpose of this report was to review the evidence on 'low' carbohydrate diets compared to current UK government advice on carbohydrate intake for adults with type 2 diabetes (T2D).

1.2 It was initiated in response to a request from Public Health England (PHE), for a systematic assessment of the scientific evidence on 'low' carbohydrate diets, in recognition that such diets are gaining attention and are increasingly being promoted. However, since there is no agreed definition of a 'low' carbohydrate diet, comparisons in this report were between lower and higher carbohydrate diets.

1.3 The Scientific Advisory Committee on Nutrition (SACN) provides advice to the UK governments on the UK general population based on its assessment of the scientific evidence. Since the Committee does not usually make recommendations relating to clinical conditions, a joint working group (WG) was established to consider this issue. The WG comprised members of SACN and members nominated by Diabetes UK, the British Dietetic Association, the Royal College of Physicians and the Royal College of General Practitioners. Representatives from NHS England and NHS Health Improvement, the National Institute for Health and Care Excellence (NICE) and devolved health departments were invited to observe the WG. The WG was jointly chaired by SACN and Diabetes UK. The secretariat for the work was provided by the SACN secretariat at PHE.

1.4 This report was developed using SACN process and signed off by SACN. It is co-badged with Diabetes UK.

Terms of reference

1.5 The terms of reference were to:

- review the evidence on lower carbohydrate diets (alongside higher fat and/or higher protein) compared to current government advice for adults with T2D
- consider the impact, in adults with T2D, of lower compared with higher carbohydrate diets on markers and clinical outcomes of T2D including any potential adverse effects
- make recommendations based on the review of the evidence.

1.6 Current UK government advice on carbohydrate intake is based on recommendations made by SACN following its review on carbohydrates and health (SACN, 2015). The evidence considered in that review comprised studies in the general population and recommendations were for the UK general population.

1.7 Current UK government advice for the general population is that approximately 50 percent (%) of total dietary energy (TE) should be obtained from carbohydrates,

mainly from starchy foods consisting of higher fibre or wholegrain foods where possible. It is recommended that average population intakes of free sugars should not exceed 5% TE and that adults should achieve a daily dietary fibre intake of 30g per day.

1.8 There are no separate recommendations on carbohydrate intake for adults with T2D and the advice for the general UK population also applies to those with T2D.

1.9 More information on carbohydrates, including definitions of free sugars and fibre, is provided in chapter 2.

1.10 The markers and clinical outcomes of T2D selected for consideration were: body weight, glycated haemoglobin (HbA1c), fasting plasma glucose, serum total cholesterol, serum triacylglycerol (also known as triglyceride), serum low density lipoprotein (LDL) cholesterol, serum high density lipoprotein (HDL) cholesterol, serum total cholesterol:HDL cholesterol ratio and medication use. Further information on these outcomes and the basis for their selection is provided in chapter 3.

1.11 The draft report was published for public consultation and comments received from interested parties were taken into consideration before the report was finalised.

1.12 The WG's remit was to assess the scientific evidence on the effects on health of lower compared to higher carbohydrate diets in adults with T2D. Its remit did not include consideration of the wider management of T2D, studies of children, people with pre-diabetes, type 1 diabetes (T1D) or gestational diabetes.

2 Background

Carbohydrates

2.1 The background information on carbohydrates summarised in this chapter is drawn from the SACN report on 'Carbohydrates and Health' (SACN, 2015), where more detailed information on carbohydrates is provided.

Classification of carbohydrates

2.2 Carbohydrates are a major source of energy in the diet and include a range of compounds, all containing carbon, hydrogen and oxygen. They are based on a common unit with varying linkages and chain lengths.

2.3 The primary classification of carbohydrates is based on chemistry, that is, the character of individual monomers, degree of polymerisation (DP) and type of linkage (α or β) (FAO/WHO, 1998). This classification divides carbohydrates into 3 main groups: sugars, including mono- and disaccharides (DP 1-2); oligosaccharides (DP 3-9); and polysaccharides (DP >9).

2.4 The 3 principal monosaccharides: glucose, fructose and galactose are the building blocks of di-, oligo-, and polysaccharides. These hexoses (6-carbon sugars) can be found in honey and fruits (the disaccharide sucrose, made up of glucose and fructose units, is also found in fruits). Galactose in combination with glucose is found in milk as lactose. Polyols (also known as sugar alcohols) include hydrogenated mono- and disaccharides used as sugar replacers. Oligosaccharides are also widely used in the food industry to modify the texture of food products. Starch is a polysaccharide of glucose monomers and is the principal carbohydrate in most diets.

2.5 Dietary fibre includes constituents of plant cell walls, such as cellulose, and is the most diverse of the carbohydrate groups. The SACN report on carbohydrates (SACN, 2015) defines dietary fibre as all carbohydrates that are neither digested nor absorbed in the small intestine and have a degree of polymerisation of 3 or more monomeric units, plus lignin.

2.6 The chemical classification of carbohydrates does not allow a simple translation into nutritional effects, since each class of carbohydrates has overlapping physiological properties and effects on health.

2.7 Carbohydrates can also be classified according to their digestion and absorption in the small intestine. Digestible carbohydrates are absorbed and digested in the small intestine. Non-digestible carbohydrates are resistant to hydrolysis in the

small intestine and reach the large intestine where they are at least partially fermented by bacteria present in the colon.

2.8 The terms ‘simple’ and ‘complex’ carbohydrates are commonly used in the literature when considering dietary carbohydrate content. However, these terms are not scientifically defined and were not used in the SACN report on carbohydrates (SACN, 2015).

2.9 The following terms are used in this report to describe carbohydrates:

- Free sugars — these include monosaccharides (glucose, fructose, and galactose) and disaccharides (which include sucrose and lactose). They refer to sugars added by food manufacturers, cooks or consumers to food and include those naturally found in honey, syrups and unsweetened fruit juice. The term does not include sugars naturally found in milk and milk products.
- Starch — polymer of glucose, found in foods such as rice, bread, pasta and potatoes.
- Dietary fibre — defined in paragraph 2.5.

2.10 The terms ‘quality’ and ‘type’ are also used in the literature to describe the nature of carbohydrates (for example, wholegrain, refined grain, free sugars, fibre). In this report the term ‘type’ is used.

Digestion and absorption

2.11 Digestion of starch begins in the mouth but takes place mainly in the small intestine where it is hydrolysed into its component monosaccharides.

2.12 Only glucose and galactose are actively absorbed in the small intestine via a sodium dependent transporter. Fructose is not actively absorbed but is taken up by a facilitative transport pathway. Di-, oligo- and polysaccharides are hydrolysed by enzymes to their component monosaccharides before they are absorbed in the small intestine.

2.13 Non-digestible carbohydrates contain glycosidic linkages that are not hydrolysed in the small intestine. They reach the large intestine where they may be fermented to some degree by commensal bacteria, which contain enzymes capable of hydrolysing those linkages (Hawksworth et al, 1971).

Metabolism

2.14 Following absorption, monosaccharides are transported to the liver and from there to the systemic circulation. The brain, nervous system and red blood cells have an obligatory requirement for glucose as an energy source.

2.15 Glucose is regulated by insulin, a hormone produced by beta-cells in the pancreas, which is released in response to glucose absorption. The plasma concentration of

insulin increases immediately after ingestion of glucose and in some tissues (for example, adipose tissue, skeletal muscle) cellular uptake of glucose is insulin-dependent. Fructose uptake into tissues is not insulin-dependent.

2.16 The amount of energy yielded by carbohydrates digested in the small intestine varies according to the molecular form; for example, the energy content per unit weight is 15.6 kJ/g (3.7 kcal/g) for glucose, 16.5 kJ/g (3.9 kcal/g) for sucrose and 17.5 kJ/g (4.2 kcal/g) for starch (Elia & Cummings, 2007). Carbohydrate that is not digested and absorbed in the small intestine may also provide energy. Fermentation in the colon results in the formation of short-chain fatty acids, some of which are absorbed into the bloodstream and are used as sources of energy.

Glycaemic index and glycaemic load

2.17 Glycaemic index (GI) and glycaemic load (GL) are measures of the post-prandial blood glucose response to foods.

2.18 GI is a relative measure of the capillary blood glucose response to a specific food compared with the response to a reference food matched for the same amount (usually 50g) of available carbohydrate (either as pure glucose or from an alternative carbohydrate food such as white bread). GI assigns a value (relative to the reference food=100) for the total increase in blood glucose over 2 hours after consumption of carbohydrate containing foods or ingredients (Jenkins et al, 1981). In general, carbohydrate sources with a low GI value (≤55), which include most intact fruits, vegetables, nuts and legumes, are more slowly digested and absorbed leading to a lower and slower rise in blood glucose and, therefore usually, insulin. Carbohydrate foods with a high GI value (≥70) cause a more substantial increase in blood glucose. High GI foods include many types of refined grain and cereal products and boiled potatoes.

2.19 A food's GL (GI multiplied by the amount of carbohydrate in a serving of that food) takes account of both the GI of the carbohydrate food and the quantity of available carbohydrate (Brouns et al, 2005).

2.20 GI and GL are predominantly influenced by the types and structures of carbohydrates present in foods and, to lesser extents, by the types and amounts of protein, fat and non-starch polysaccharide present. External influences affecting the GI and GL of a food include milling, cooking, cooling and storage conditions (Brouns et al, 2005; Venn & Green, 2007).

Definitions of diets containing different amounts of carbohydrate

2.21 There is no clear consensus on the definition of a 'low carbohydrate diet' which varies widely across studies. Feinman et al (2015) proposed definitions for diets

containing different amounts of carbohydrate categorised as ‘very low’, ‘low’, ‘moderate’ or ‘high’ (adapted from Accurso et al, 2008). These categories are defined in both grams per day and as a percentage of TE intake of approximately 2,000 kcal/day (see Table 2.1).

2.22 For the purposes of this report, in order to enable comparisons of carbohydrate intakes across the studies under consideration, the classification proposed by Feinman et al (2015) was adopted as the basis for categorisation of carbohydrate intake.

Table 2.1: Categories of dietary carbohydrate intakes[1]

Carbohydrate category	Amount of carbohydrate	
	g/day	**% TE** (based on 2000 kcal/day)
Very low[2]	20 to 50	≤10
Low	>50 to <130	>10 to <26
Moderate	130 to 230	26 to 45
High	>230	>45

[1] Based on Feinman et al (2015) and Accurso et al (2008)
[2] Also referred to as ketogenic diets

2.23 According to the above categories, government recommendations on carbohydrate intake for the general population (50% TE) would be classified as ‘high’.

2.24 Categorisation of a ‘low’ carbohydrate diet varies between studies with some defining it in g/day and some as % TE. In weight loss interventions carbohydrate intakes might be relatively low in terms of g/day but relatively high in terms of % TE. This is also the case with low and very low energy diets (see next paragraph) which may be low in reported g/day of carbohydrate but also low in other macronutrients and, therefore, relatively high in carbohydrates as % TE.

2.25 ‘Low’ and ‘very low’ carbohydrate diets should not be confused with low and very low energy diets (also known as low and very low calorie diets). Low energy diets provide 800 to 1200 kcal/day and include diets based on food or on meal replacements (formulated products such as shakes, soups, bars). Very low energy diets provide <800 kcal/day (Codex Alimentarius, 1995; NICE, 2014). The majority are made of formulated products to ensure adequate protein and micronutrient intake.

Type 2 Diabetes

2.26 Diabetes is a condition in which the body does not produce sufficient insulin to regulate blood glucose concentrations and the insulin produced does not work effectively. This leads to elevated blood glucose concentrations (hyperglycaemia) which causes damage to blood vessels and nerves.

2.27 There are two main types of diabetes: type 1 diabetes (T1D) and type 2 diabetes (T2D). There are also other forms such as gestational diabetes and rare genetic forms such as maturity onset diabetes of the young (MODY).

2.28 In 2018, an estimated 4.7 million people in the UK had diabetes (Diabetes UK, 2019). This included about 3.8 million people with diagnosed diabetes and an estimated 1 million people who were undiagnosed.

2.29 T1D accounts for about 8% of all cases of diabetes in the UK (NHS Digital, 2018; NHS Scotland, 2018; Diabetes UK, 2019). It occurs as a result of autoimmune beta-cell destruction, usually leading to absolute insulin deficiency (ADA, 2019). T1D, gestational diabetes and MODY are not considered further in this report.

2.30 T2D accounts for about 90% of all cases of diabetes in the UK (NHS Digital, 2018; NHS Scotland, 2018; Diabetes UK, 2019) and occurs as a result of reduced beta-cell insulin secretion and increased insulin resistance (ADA, 2019). Although several non-modifiable risk factors such as age, family history and ethnicity are associated with increased T2D risk, about 80 to 85% of an individual's risk of developing T2D is associated with overweight (body mass index (BMI) ≥25 to <30 kg/m$^{2)}$ and obesity (BMI ≥30 kg/m^2) (Hauner, 2010), a modifiable risk factor.

2.31 Symptoms of diabetes include frequent urination, extreme thirst, tiredness, unplanned weight loss and infection such as genital thrush. About 60% of people with T2D do not have any symptoms when they are diagnosed (Winkley et al, 2013). Consequently, 1 in 3 people may develop complications with their eyes, feet, kidneys or nerves by the time they are diagnosed (Winkley et al, 2013); so early diagnosis and treatment is vital.

2.32 Diagnosis of T2D is based on elevated blood glucose concentrations or an elevated HbA1c concentration (often reported as a percentage of red blood cells that are glycated). These indices are markers of impaired control of blood glucose and associated metabolic processes (usually referred to as impaired glycaemic control).

2.33 In the UK, the cut-off HbA1c concentration for T2D diagnosis is 48 mmol/mol (6.5%) (WHO, 2011). HbA1c concentrations for non-diabetic hyperglycaemia are between 42 and 47.9 mmol/mol (6.0 to 6.4%), and concentrations below 42 mmol/mol (6.0%) are regarded as non-diabetic (NICE, 2017). The cut-off for fasting plasma glucose concentration for T2D diagnosis is 7.0 mmol/L (or post prandial concentration of 11.1 mmol/L) (WHO, 2006) with concentrations between

6.1 and 6.9 mmol/L reflecting non-diabetic hyperglycaemia and 6.0 mmol/L or less as normal glycaemia (NICE, 2017).

2.34 Elevated blood glucose concentrations over time can have serious long-term consequences such as heart attacks, strokes, kidney diseases, blindness, lower-limb amputations and premature death. Cardiovascular diseases (CVD) are the leading cause of death for people with T2D. Every year in the UK, T1D and T2D are linked to more than 27,000 heart attacks (NHS Digital, 2017; SSNAP, 2019), 35,600 strokes (NHS Digital, 2017; SSNAP, 2019) and 8,793 amputations (NCVIN, 2018). In the UK, more than 1,300 people every year have their eyesight seriously affected by their diabetes (PHE, 2019) and at least 10,375 people have end-stage kidney failure caused by their diabetes (Byrne et al, 2018).

2.35 Individuals from minority ethnic population groups are at higher risk of T2D. According to the 2004 Health Survey for England (n=13,300) T2D prevalence was higher in Black Caribbean (9.5% men, 7.6% women), Indian (9.2% men, 5.9% women), Pakistani (7.3% men, 8.4% women), and Bangladeshi (8.0% men, 4.5% women) populations compared to the general population (3.8% men, 3.1% women). An analysis of primary care data from London (n=404,318) reported that, after adjusting for differences in age group, sex and social deprivation, all minority ethnic population groups were more likely to have a T2D diagnosis compared with the White group (more than double among Asian people, 65% more among Black people, and 17% more among people of Mixed or Other ethnicities) (Pham et al, 2019).

UK and international recommendations for management of T2D

2.36 In England, NICE has issued guidelines for the identification, diagnosis and management of T2D (NICE, 2020). The Scottish Intercollegiate Guidelines Network (SIGN) have also issued guidelines on management of diabetes (SIGN, 2017).

2.37 The ultimate aim of T2D management and treatment is to reduce and maintain HbA1c concentration at a value below the cut-off for the definition of T2D. However, any reduction in HbA1c reflects an improvement in the degree of T2D control. Reduction of blood lipids and blood pressure are also important treatment goals.

2.38 Management of T2D usually involves behavioural interventions (including diet, physical activity, smoking cessation, reduced alcohol intake) and/or medications. Treatment may also include bariatric surgery to reduce weight.

2.39 There is currently no cure for T2D but data from weight management programmes and bariatric surgery confirm that weight loss can result in remission (HbA1c <48 mmol/mol or 6.5% for ≥6 months) (Diabetes UK, 2018b). The DiRECT study, a UK

primary care-led weight management intervention for people with T2D (of less than 6 years duration), reported 46% remission at 1 year and 36% remission at 2 years (Lean et al, 2019). An international consensus statement endorsed by 45 international diabetes associations including Diabetes UK and the American Diabetes Association (ADA) also reported that T2D remission generally occurs in about 30 to 63% of patients 1 to 5 years following bariatric surgery (Rubin et al, 2016) and a remission rate of about 30% has been reported at 15 years following surgery (Sjostrom et al, 2014).

Dietary management of T2D

2.40 A reduction in energy (calorie) intake is an important part of the behavioural interventions recommended to people with T2D who are living with overweight or obesity. The aim of reducing energy intake is weight loss, which in turn improves glycaemic control. For example, NICE (2020) recommends setting an initial body weight loss target of 5 to 10% for those living with overweight (BMI ≥25 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2).

2.41 Dietary changes, such as a reduction in saturated fat and substitution with unsaturated fats, are also generally recommended in order to reduce CVD risk (SACN, 2019).

2.42 In England, NICE (2020) recommends a healthy balanced dietary pattern that is applicable to the general population, for people with T2D. This reflects current government advice for the general population (including those with T2D) for a carbohydrate intake of approximately 50% TE. Current government advice for the general population is outlined in Annex 1 (Table A1.1) and is based on SACN recommendations (SACN, 2015). NICE (2020) also recommends providing individualised advice and encouraging 'high fibre, low glycaemic index sources of carbohydrate in the diet such as fruit, vegetables, wholegrains and pulses; include low fat dairy products and oily fish; and control the intake of foods containing saturated and trans fatty acids'.

2.43 SIGN (2017) recommends that individuals with T2D 'are given dietary choices for achieving weight loss that may also improve glycaemic control. Options include energy restriction, reducing fat intake, consumption of carbohydrates with low rather than high GI, and restricting the total amount of dietary carbohydrate (a minimum of 50 g per day appears safe for up to six months)'.

2.44 International guidelines vary in relation to the amount of carbohydrate recommended for people with T2D (see Table 2.2, below). Diabetes UK, the ADA and Diabetes Australia have made dietary recommendations that focus on foods and overall dietary patterns.

2.45 Diabetes Australia recommends following the Australian Dietary Guidelines for Adults (Diabetes Australia, 2015). In a position statement on low carbohydrate

eating for people with diabetes, it states ‘there is reliable evidence that lower carb eating can be safe and useful in lowering average blood glucose levels over the short term (up to 6 months)’ and that it can ‘also help reduce body weight and help manage heart disease risk factors such as raised cholesterol and raised blood pressure’ (Diabetes Australia, 2018).

2.46 Both Diabetes UK and the ADA emphasise tailoring advice to the individual and both note the lack of clear evidence for a specific dietary intake of carbohydrate for those with T2D (Diabetes UK, 2018a; ADA, 2020). The ADA notes that ‘reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences’ and that ‘for individuals with type 2 diabetes not meeting glycaemic targets or where reducing antihyperglycemic medications is a priority, reducing overall carbohydrate intake with low or very-low carbohydrate eating plans is a viable approach’.

2.47 Diabetes Canada (2020), in a position statement on low carbohydrate diets for people with Diabetes, recommends that ‘healthy’ low- or very-low carbohydrate diets can be considered as one healthy eating pattern for individuals living with T2D and those ‘who prefer to adopt a low- or very low-carbohydrate dietary pattern, should be encouraged to consume a variety of foods’.

2.48 International organisations consistently recommend carbohydrates low in free sugars and high in fibre, such as those found in vegetables and fruit, wholegrains and legumes including lentils and pulses (SACN, 2015; USDHHS & USDA, 2015; Reynolds et al, 2019). Carbohydrates that are associated with poorer health outcomes include sugars, especially sugar-sweetened beverages and carbohydrates refined or processed in ways that raise the free sugars content or reduces the levels of naturally occurring fibres, and it is recommended that these foods are limited (SACN, 2015; USDHHS & USDA, 2015).

2.49 Macronutrient recommendations for adults with T2D, from NICE, SIGN and a range of diabetes organisations are summarised in Table 2.2 below.

Table 2.2: UK and international macronutrient recommendations for adults with T2D

Organisation	Macronutrient (% TE)		
	Carbohydrate	Total fat	Protein
NICE*	50	35	
SIGN	Individualise	Individualise	
Diabetes UK	Individualise (low carbohydrate diets** amongst other strategies, for weight loss in the short term)	No specific amount	No specific amount
ADA	Individualise (low carbohydrate diets viable option for reducing blood sugar levels or anti-hyperglycaemic medication)	Individualise	Individualise
Diabetes Canada	45 to 60	≤35	15 to 20
European Association for the Study of Diabetes	45 to 60	≤35	10 to 20
Diabetes Australia	No specific amount (low carbohydrate diets** amongst other strategies for reducing blood sugar levels and weight loss in the short term (6 months)	No specific amount	No specific amount

* NICE guideline [NG28] recommendation adapted to be in line with UK government advice.

** Defined as <130g/day or <26% TE from carbohydrate.

Data from Diabetes UK (2018a), SIGN (2017), ADA (2020), Diabetes Canada (2020), Mann et al (2004), Diabetes Australia (2015), Diabetes Australia (2018),(NICE, 2020).

Evidence from clinical practice

2.50 A number of clinical studies (for example, Saslow et al (2017); Bhanpuri et al (2018); Hallberg et al (2018); Saslow et al (2018); Athinarayanan et al (2019)) and case reviews (for example, (Unwin & Tobin, 2015)) have considered the effectiveness of lower carbohydrate diets on glycaemic control and other markers in adults with T2D. Many of these studies are based in primary or secondary care clinical practice settings. Some provide commercial very-low carbohydrate ketogenic diet programmes or use data from participants self-enrolled in dietary programmes.

2.51 Information from these studies, overall, indicates that low carbohydrate diets can be beneficial in reducing weight and improving glycaemic control and may also lead to reductions in medication use.

2.52 The research design of these studies has varied but includes non-randomised trials, single-arm trials with no control group, quasi-experimental studies, or described experiences in clinical practice. When a control group has been used, the intervention and control arms have generally not been balanced (see paragraph 2.54).

2.53 Clinical practice studies and case reviews were not considered in this report because they did not meet the inclusion criteria for study selection (see paragraphs 4.3 to 4.5). However, evidence from these studies can supplement information obtained from RCTs. For example, they can address adherence and treatment preferences of adults with T2D. They can also be helpful for generating hypotheses and informing the design of future RCTs. However, clinical practice studies are generally not included in evidence reviews to inform policies at the population level because of important limitations (see below), considerable risk of bias and challenges in their interpretation.

2.54 A key limitation in clinical practice studies that include a comparator group is lack of randomisation. Participants may be offered the choice of selecting the treatment group and choose (or be assigned to) a study or study arm for a variety of reasons (for example, their dietary preference, age, sex or ethnicity) which could lead to systematic differences between groups. There may also be variation between study arms such as differences in sample size and intensity of intervention. An unbalanced sample size, for example larger numbers of participants in the intervention group, could provide more power to detect associations within the intervention group and any lack of effect in the comparator group could be due to insufficient statistical power. Often there is greater frequency of contact and intensity of monitoring in the intervention group; therefore any observed effects may not be solely ascribed to a change in diet but could in part be due to more intensive behavioural support in the intervention group (Singh et al, 2019).

2.55 An important limitation in studies without a comparator group is that it is not possible to assess whether an alternative diet plan would be more or less effective. Interpretation is limited to the effectiveness of the diet and behavioural advice package in the group that voluntarily chose to follow that plan. In cases where individuals are paying fees for the diet plan, they are self-selected and more likely to be motivated towards adherence to that specific plan and the findings may not be generalisable.

2.56 In many of these studies, especially web-based remote interventions, the analysis is limited to the small percentage of people who remain in the programme, which may lead to bias. In addition, self-reporting of glycaemic control and other markers might lead to greater measurement error.

2.57 For the reasons outlined above, evidence from clinical practice is not comparable to evidence from RCTs.

3 Markers and clinical outcomes of type 2 diabetes

3.1 The primary outcomes considered in this review are change in body weight (≥12 months) and HbA1c (≥3 months).

3.2 The secondary outcomes considered are change in body weight (≥3 to <12 months), fasting plasma glucose (≥3 months), blood lipids (≥3 months) and medication use.

3.3 One of the aims of dietary management for people with T2D is to reduce the risk of CVD. Weight loss has beneficial effects on a number of CVD risk factors, including high blood pressure. In contrast with blood lipids, changes in dietary macronutrient composition were not expected to have independent effects on blood pressure. Instead, weight loss is likely to be the primary driver for any decrease in blood pressure associated with lower carbohydrate diets. Blood pressure was therefore not included as an outcome measure. However, blood pressure reduction is an important factor that should be considered in the overall health of adults with T2D since it can contribute to reductions in CVD risk (WHO, 2007).

3.4 Data were grouped according to shorter-term (minimum duration of 3 months) and longer-term (minimum duration of 12 months) measurements.

Primary outcomes

Body weight (≥ 12 months)

3.5 Ninety percent of adults with T2D in the UK are living with overweight or obesity (Diabetes UK, 2018c). Interventions aim, therefore, to support people to achieve and maintain a healthy body weight. Many shorter-term interventions are able to achieve weight loss but the maintenance of weight loss is challenging (Miller & Brennan, 2015). Therefore, for body weight as a primary outcome, only studies with a minimum duration of 12 months were assessed and included in the draft report when it was published for public consultation (see paragraph 4.10).

3.6 Following consideration of comments received in response to the public consultation it was subsequently agreed to include consideration of shorter-term (≥3 to <12 months) studies on body weight as a secondary outcome.

HbA1c

3.7 An elevated HbA1c concentration is a marker of impaired glycaemic control. The aim of T2D management is to improve glycaemic control because a reduction in

HbA1c concentration indicates an improvement in control of T2D and a reduction in risk of long-term complications.

3.8 Since the life-cycle of red blood cells (that contain haemoglobin) in the circulation is approximately 100 to 120 days, the most clinically meaningful changes in HbA1c will be found after a period of around 3 months. Only studies with a minimum duration of 3 months were therefore considered in this report.

Secondary outcomes

Body weight (≥3 to <12 months)

3.9 Shorter-term (≥3 to <12 months) change in body weight was considered as a secondary outcome (see paragraph 3.6).

Fasting plasma glucose

3.10 HbA1c was the primary outcome related to glycaemic control considered in this review; however, some of the research literature also reports impacts on fasting plasma glucose (especially older studies that may have based the definition of diabetes on measurement of fasting plasma glucose concentrations). Fasting plasma glucose was therefore considered as a secondary outcome.

Blood lipids

3.11 T2D is a major risk factor for CVD which is the principal cause of death in individuals with T2D. One of the contributors to this high risk is dyslipidaemia, a condition where there is an abnormal amount of lipids (such as non-HDL cholesterol and triacylglycerols) in the blood. Dyslipidaemia increases the risk of a number of metabolic diseases including CVD (SACN, 2019). Increased concentration of serum HDL cholesterol is associated with reduced risk of CVD (SACN, 2019).

3.12 To assess the effects of lower carbohydrate diets on fasting lipid profiles in people with T2D, the following markers were considered: serum total cholesterol, serum triacylglycerol, serum LDL cholesterol, serum HDL cholesterol, and serum total cholesterol:HDL cholesterol ratio. Beneficial effects would include reductions in total cholesterol, serum LDL cholesterol, serum triacylglycerol, serum total cholesterol:HDL cholesterol ratio and an increase in serum HDL cholesterol.

Medication use

3.13 A successful intervention goal for people with T2D would be a reduction in T2D medication (for managing levels of glycaemia, blood pressure and blood lipids). A dietary intervention would be considered beneficial if it was able to achieve the same level of glycaemic control with a reduced need for diabetes medication.

4 Methods

4.1 This report is based on evidence provided by systematic reviews (SRs) and meta-analyses (MAs). This is because SRs and MAs reduce the potential for biased study selection or overlooking relevant studies since they are systematic and provide a comprehensive and quantitative analysis of the research in a particular field.

4.2 The evidence was assessed using SACN's Framework for the Evaluation of Evidence (SACN, 2012). The framework is based on an evidence hierarchy which ranks the strength of the evidence according to study design. More weight is placed on evidence from RCTs since well-conducted RCTs minimise the potential for selection bias and confounding. Less weight is placed on observational studies because they are potentially subject to bias, confounding and reverse causality. However, in the absence of RCTs, evidence from non-randomised intervention studies and prospective studies is considered stronger than that from other study designs (case-control, cross-sectional and case reports).

Evidence review process

Inclusion criteria

4.3 The following types of studies were included: SRs, MAs and pooled analyses of RCTs and prospective cohort studies comparing the impact of lower versus (vs) higher carbohydrate diets on markers and clinical outcomes of T2D (see chapter 3); RCTs published after the most recent SRs, MAs and pooled analyses of RCTs.

4.4 Additional eligibility criteria included: English language publications with no geographical restriction, published in peer-reviewed scientific journals after 1980 (since very few studies before then measured HbA1c).

4.5 Only SRs that included studies with a minimum duration of 3 months and individuals with pre-diagnosed T2D (as defined in the primary RCTs) when they entered the study were considered.

Exclusion criteria

4.6 The following types of studies were excluded: SRs and MAs of case-control or cross-sectional studies, non-SRs, case reports, published abstracts, grey literature such as dissertations, conference proceedings, magazine articles, books or book chapters, opinion pieces, information from websites, reports and other non-peer reviewed articles.

4.7 Studies with mixed populations (for example, individuals with T1D or metabolic syndrome or with pre-diabetes) in which results were not presented separately for T2D were also excluded.

Literature search

4.8 The PHE Knowledge and Library Services team conducted an online database search. MEDLINE, EMBASE, the Cochrane Library (CDSR and DARE), NICE evidence, TRIP and Google Scholar were searched, using the search terms outlined in Annex 2 (Table A2.1), for relevant publications meeting the inclusion criteria (see paragraph 4.3 to 4.5). Interested parties were invited to highlight any additional evidence (which met the inclusion criteria) to that identified by the PHE literature search in a call for evidence published on the SACN website (from 9 February to 7 March 2018).

4.9 The agreed cut-off date for consideration of any further newly published eligible evidence (see paragraphs 4.3 to 4.5) was 30 September 2018.

4.10 In addition, the draft report was published for public consultation (from 5 March to 30 April 2020) and interested parties were invited to alert SACN to any evidence it may have missed.

4.11 Relevant evidence identified through the consultation process or published after 30 September 2018 (see paragraph 4.9) was considered by the WG.

4.12 It was agreed that the draft report would be amended only if any evidence identified after 30 September 2018 or through the consultation process was judged to have an important bearing on the conclusions.

Selection of studies

4.13 Two reviewers independently screened titles and abstracts of the publications identified by the literature search and subsequently assessed full text articles. Any differences were resolved by consensus.

4.14 After removal of duplicates (n=1491), the online database search identified 3169 abstracts which were screened for eligibility. Publications were rejected if it could be determined from the titles and abstracts that they did not meet the inclusion criteria.

4.15 Full texts of 19 potentially relevant SRs with MAs were retrieved and assessed. Out of these, 15 were excluded. Details of the excluded SRs with MAs and the reasons for their exclusion are provided in Annex 3 (Table A3.1).

4.16 Five additional publications that met the inclusion criteria were identified by WG members: 4 SRs with MAs and 1 network meta-analysis (NMA).

4.17 The primary studies in all the SRs with MAs and the NMA were RCTs. No SRs of prospective cohort studies were identified.

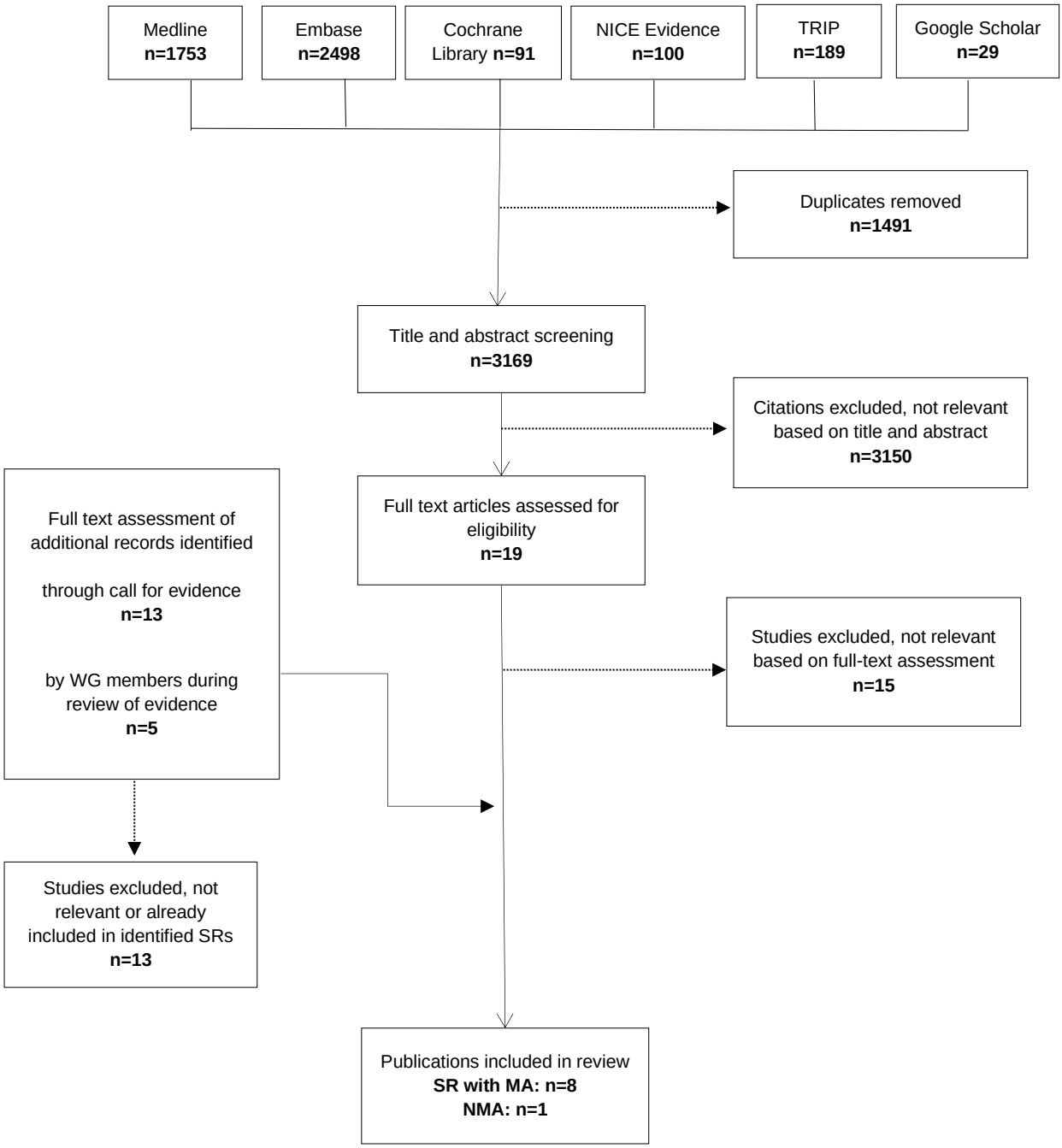
4.18 Thirteen publications were cited in responses received to the call for evidence (Annex 3, Table A3.2). Out of these, 2 RCTs (Saslow et al, 2017; Tay et al, 2018) published after the NMA which had the most recent search period (Schwingshackl et al, 2018), met the inclusion criteria. However, they were not considered separately in the evidence review because the RCT by Tay et al (2018) was included in one of the identified SRs with MAs (van Zuuren et al, 2018) (see next paragraph) and the RCT by Saslow et al (2017) was included in a SR with MA (McArdle et al, 2018) published after 30 September 2018 (see paragraph 4.21 below).

4.19 In total, 8 SRs with MAs (Naude et al, 2014; Fan et al, 2016; Meng et al, 2017; Snorgaard et al, 2017; Huntriss et al, 2018; Korsmo-Haugen et al, 2018; Sainsbury et al, 2018; van Zuuren et al, 2018) and 1 NMA (Schwingshackl et al, 2018) were included for detailed assessment.

4.20 The process for study selection and inclusion is displayed in Figure 4.1 below.

4.21 Three additional SRs with MAs (McArdle et al, 2019; Silverii et al, 2020; Goldenberg et al, 2021) and 1 NMA (Neuenschwander et al, 2019) were identified after the cut-off date for consideration of the evidence (30 September 2018). These publications were not included in the initial review of the evidence (see chapter 5) but were considered alongside, or subsequent to, comments received to the public consultation on the draft report (see paragraph 4.10). The findings of the 3 SRs with MAs and the NMA (summarised in Annex 4, Tables A4.1 to A4.2) did not alter the draft conclusions.

Figure 4.1: Flow diagram showing the number of publications assessed for eligibility and included in the evidence review (described in paragraphs 4.14 to 4.19)



Data extraction

Eligible SRs with MAs and NMA

4.22 The following data were extracted from the 8 eligible SRs with MAs and the NMA (see Annex 5, Tables A5.1 to A5.2): first author, year of publication, research question, study design, location, funding, declarations of interest, inclusion and exclusion criteria, statistical analysis, assessment of study quality, total number of primary RCTs, total number of participants, study duration, demographics and results.

Primary publications in the 8 eligible SRs with MAs

4.23 In total, there were 48 publications (relating to 43 primary RCTs) included in the 8 eligible SRs with MAs. Information (see paragraph 4.25) was extracted from all 48 publications to enable a more detailed assessment and interpretation of the evidence (see Annex 6, Tables A6.1 to A6.3).

4.24 Information was not extracted from the primary studies (n=56) included in the NMA (Schwingshackl et al, 2018) since it assessed the comparative efficacy of a range of different dietary approaches in the management of T2D and many of the component studies did not compare lower and higher carbohydrate diets.

4.25 Data extracted from the publications in the 8 eligible SRs with MAs included: sample size; age; inclusion and exclusion criteria; study power; intervention duration; loss to follow-up; type of analysis, intention-to-treat (ITT) or per protocol (PP); outcomes; funding sources; prescribed and reported intakes of carbohydrates; dietary fat including saturated fats (SFA), polyunsaturated fats (PUFA) and monounsaturated fats (MUFA) and protein; prescribed and reported intakes of energy; T2D duration and T2D inclusion criteria, medication use; and recommendations for physical activity.

4.26 Where primary RCTs included multiple comparator arms, data for the higher carbohydrate groups were pooled to create one comparator diet group. Where carbohydrate intakes were reported as a range, the average value was estimated.

4.27 The overlap of publications included in the 8 SRs with MAs, grouped by outcome, are tabulated in Annex 7 (Tables A7.1 to A7.7).

4.28 The extracted data (see paragraph 4.25) were used to prepare bar graphs showing the following comparisons between the lower and higher carbohydrate groups for the primary outcomes (body weight at ≥ 12 months and HbA1c) (see Annex 8, Figures A8.1 to A8.20):

- prescribed and reported carbohydrate intakes
- difference between carbohydrate intakes (prescribed vs reported)
- adherence to prescribed carbohydrate intakes

- macronutrient (carbohydrate, fat, protein) intakes
- energy intakes
- fatty acid intakes (SFAs, PUFAs, MUFAs)

Units of measurement

4.29 Energy intakes were expressed in kilocalories (kcal) with the corresponding SI (International system of units) values in kilojoules (kJ) in brackets. Where energy intakes were expressed in kJ, they were converted to kcal for consistency (1 kJ = 0.239006 kcal).

4.30 HbA1c values were expressed as percentages since this is how they were reported in the primary RCTs included in the SRs with MAs. The corresponding SI units (mmol/mol) were also included in brackets for information. The following formula was used to convert units for HbA1c from percentage to mmol/mol: HbA1c (mmol/mol) = [HbA1c (%) - 2.15] × 10.929 (NGSP, 2010).

4.31 Concentrations of serum total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerol and plasma glucose were expressed as mmol/L. Where concentrations were reported in mg/dL they were converted to mmol/L using the following formulae:

- serum total cholesterol, LDL cholesterol and HDL cholesterol, 1 mmol/L = 38.61 mg/dL
- serum triacylglycerol, 1 mmol/L = 88.5 mg/dL
- plasma fasting glucose, 1 mmol/L = 18 mg/dL

4.32 Carbohydrate intakes (prescribed and reported) were expressed as a percentage of TE. Where carbohydrate intakes were reported as g/day, values for energy intake were used to estimate carbohydrate as % TE (1 g of carbohydrate = 4 kcal).

Process for assessment of the evidence

Evaluation of the quality of the evidence

4.33 The quality of the 8 eligible SRs with MAs was assessed using:

- SACN Framework for the Evaluation of Evidence (SACN, 2012)
- AMSTAR 2 (a measurement tool to assess systematic reviews) (Shea et al, 2017).

SACN Framework

4.34 The following criteria were considered:

Systematic review and meta-analyses

- scope and aims
- search dates (publication dates of included studies)
- inclusion and exclusion criteria
- number of primary studies and total number of participants
- conduct and reporting of pre-specified outcomes consistent with registered protocol.

Primary studies within systematic reviews and meta-analyses

- exposure and intervention duration and follow-up
- types of carbohydrates (for example, starch, free sugars, fibre) and types of macronutrients replacing carbohydrates in the lower carbohydrate groups
- prescribed and reported intakes of carbohydrates in lower and higher carbohydrate groups
- populations considered and relevant characteristics (duration of known T2D, medication use, physical activity levels).

Interpretation of results and analysis

- appropriateness of statistical methods used
- whether and which confounding factors were taken into account (where relevant)
- consistency of the effect (taking account of overlap in the primary studies considered)
- heterogeneity: an I^2 statistic of 0 to 25% was considered to represent low heterogeneity; 26 to 75%, medium heterogeneity; and >75%, high heterogeneity. While a high I^2 statistic reflects uncertainty regarding the value of the pooled estimate, it does not necessarily reflect uncertainty regarding the direction of the effect or association (which may be consistent across studies)
- direction and size of effect and statistical significance
- results of subgroup and sensitivity analyses.

4.35 In accordance with the SACN Framework for the Evaluation of Evidence, the word ‘effect’ was used to describe the evidence from RCTs. An effect was deemed to be statistically significant using the two-tailed $p<0.05$ criterion.

AMSTAR 2

4.36 The methodological quality of each eligible publication was assessed independently by 2 members of the secretariat and a member of the WG and any differences were resolved by consensus.

4.37 AMSTAR 2 comprises 16 items for evaluation (AMSTAR, 2017) which are listed in Box 4.1 below:

Box 4.1: AMSTAR 2 criteria for evaluation

1. Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, control group, outcome)?
2. Did the report of the review contain an explicit statement that review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If MA was performed, did the review authors use appropriate methods for statistical combination of results?
12. If MA was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the MA or other evidence synthesis?
13. Did the review authors account for risk of bias in primary studies when interpreting/discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

4.38 In addition to the items identified as critical by AMSTAR 2 (items 2, 4, 7, 9, 11, 13 and 15), the WG agreed that item 8 should also be considered critical because detailed information about the included studies (duration, sample size, loss to follow-up), the population (such as medication use, duration since diabetes diagnosis, physical activity) and the intervention (such as prescribed and reported intakes of carbohydrate, dietary advice, approach, adherence) would be important for assessment and interpretation of the evidence.

4.39 Item 3 was not considered since all the selected SRs with MAs included only RCTs which is the preferred study design in the SACN Framework (2012).

4.40 A summary of the AMSTAR 2 assessment is provided in Annex 9 (Table A9.1).

Approach to considering statistical models

4.41 The results of 2 statistical models of MA, fixed effects and random effects, are increasingly being reported in SRs with MAs. There are differences in the underlying assumptions and statistical considerations of the models. Random-effects models generally give proportionally more weight to small than to large primary studies, while fixed-effects models give weight in direct proportion to the size of the primary studies. However, the choice of models and their interpretation remains an area of debate among statisticians (SACN, 2019). More detailed information on the 2 models is available in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al, 2021).

4.42 The following approach, used by SACN in its report on 'Saturated Fats and Health' (SACN, 2019), was used when considering the MAs:

- Where results of only 1 model (that is, fixed effects or random effects) were stated, these were reported and used to draw conclusions.
- Where results of both models were stated, both were reported. The following factors were considered: appropriateness of the model assumptions, direction and magnitude of the effect, statistical significance and level of agreement between the models. Where the results of the 2 models differed, the totality of the evidence and expert judgement were used to draw conclusions and considered in the final grading of the evidence (see below).

Grading of the evidence

4.43 The methods outlined in the SACN reports on Carbohydrates and Health (SACN, 2015) and Saturated Fats and Health (SACN, 2019) were modified for use in this report.

4.44 Expert judgement, based on the criteria specified in Table 4.1 below, was used to grade the strength of the evidence (**adequate, moderate, limited, inconsistent** or **insufficient**) for the primary and secondary outcomes.

4.45 Emphasis was placed on results of the largest (based on number of participants) MA. If these results disagreed with those of other MAs, then this was reported.

4.46 When evaluating consistency and agreement between the MAs, consideration was given to statistical significance, direction and magnitude of effect size, subgroup and sensitivity analyses, heterogeneity and the degree of overlap in the primary studies.

4.47 Risk of bias was taken into account through use of SACN and AMSTAR 2 criteria (see above sections) to inform the consideration of SR quality. The risk of bias of individual RCTs described within each SR, was also used to inform the criteria described in Table 4.1. The potential for publication bias was minimised by placing emphasis on the largest MA. Consideration was also given to any sensitivity analysis excluding individual RCTs with high risk of bias.

4.48 Only outcomes where the evidence base was graded as **adequate** or **moderate** were used to inform recommendations.

Table 4.1 Criteria for grading evidence (SACN, 2019)

Strength of evidence	Explanatory notes
Adequate	There is **adequate** evidence to make a decision about the effect or association of a factor(s) or intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, evidence from meta-analyses goes in the same direction. Results of meta-analyses are statistically significant or, in systematic reviews without meta-analysis, there is convincing evidence of a consistent significant effect or association in the primary studies considered. Effects or associations are also consistent when major population subgroups or other relevant factors are considered in additional analyses. The identified publications are considered to be of good quality based on the key factors listed above. The inclusion and exclusion criteria of the identified publications are well defined and appropriate. A judgement of **adequate** evidence is also made based on the number, size, quality and durations or follow-ups of RCTs and/or

Strength of evidence	Explanatory notes
	prospective cohort studies included in the identified systematic reviews, meta-analyses and pooled analyses. Where only 1 systematic review, meta-analysis or pooled analysis is identified on a specific outcome, evidence is considered **adequate** if the publication reports primary data from ≥ 3 RCTs or ≥ 5 cohort studies, of adequate size, considered to be of good quality and which were included in a meta-analysis or pooled analysis. Alternatively, for a single systematic review without a meta-analysis or pooled analysis, evidence may be considered **adequate** if a total of ≥ 4 RCTs or ≥ 5 cohort studies, of adequate size and considered to be of good quality, consistently went in the same direction.
Moderate	There is **moderate** evidence (therefore less conclusive) to make a decision about the effect or association of a factor(s) or intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, the majority of the evidence from meta-analyses goes in the same direction. The results of meta-analyses are statistically significant or, in systematic reviews without meta-analysis, there is moderate evidence of a consistent significant effect or association in the primary studies considered. Effects or associations may be less consistent when major population subgroups or other relevant factors are considered in additional analyses. The identified publications are considered to be of moderate to good quality based on the key factors listed above. The inclusion and exclusion criteria of the identified publications are reasonably well defined and generally appropriate. Compared to evidence considered adequate, there may be fewer and smaller RCTs and/or prospective cohort studies, of moderate quality with sufficient durations or follow-ups, included in the identified systematic reviews, meta-analyses and pooled analyses. Where only 1 systematic review, meta-analysis or pooled analysis is identified on a specific outcome, evidence is considered **moderate** if the publication reports primary data from ≥3 RCTs or

Strength of evidence	Explanatory notes
	3-4 cohort studies of moderate size, considered to be of moderate quality and which were included in a meta-analysis or pooled analysis. Alternatively, for a single systematic review without a meta-analysis or pooled analysis, evidence may be considered **moderate** if a total of ≥ 3 RCTs or 5 cohort studies, of moderate size and considered to be of moderate quality, consistently went in the same direction.
Limited	There is **limited** evidence (therefore, even less conclusive) to make a decision about the effect or association of a factor(s) or intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, the majority of the evidence from meta-analyses goes in the same direction. The results of meta-analyses are statistically significant or, in the case of systematic reviews without meta-analysis, there is limited evidence of a consistent significant effect or association in the primary studies considered. Effects or associations may be inconsistent when major population subgroups or other relevant factors are considered in additional analyses. The identified publications are considered to be of poor to moderate quality based on the key factors listed above. The inclusion and exclusion criteria of the identified publications are not well defined and may not be appropriate. Compared to evidence considered **adequate** or **moderate**, there may be fewer and smaller RCTs and/or prospective cohort studies, of low quality with inadequate durations or follow-ups, included in the identified systematic reviews, meta-analyses and pooled analyses. Where only 1 systematic review, which did not include a meta-analysis, is identified on a specific outcome, evidence was considered **limited** if primary data from 3-4 RCTs or prospective cohort studies of limited size and considered to be of low quality were identified but there was some evidence that the results were in the same direction.

Strength of evidence	Explanatory notes
Inconsistent	There is **inconsistent** evidence after taking into account the above quality criteria and overlap of primary studies included in the identified systematic reviews, meta-analyses and pooled analyses. The results in relation to a specific outcome are conflicting and it is not possible to draw conclusions.
Insufficient	There is **insufficient** evidence as a result of no systematic reviews, meta-analyses or pooled analyses of appropriate quality identified in relation to a specific outcome or, in a single review or analysis, <3-4 eligible RCTs or cohort studies were identified. Therefore, it is not possible to draw conclusions.

Prioritisation of evidence

4.49 After detailed assessment of the 8 eligible SRs with MAs, the results of MAs from 4 were prioritised and used to grade the evidence and to draw conclusions (Huntriss et al, 2018; Korsmo-Haugen et al, 2018; Sainsbury et al, 2018; van Zuuren et al, 2018). This is because they were more recent, had larger numbers of participants and were considered to be of better quality (based on SACN and AMSTAR 2 criteria; see paragraphs 4.34 to 4.38 and Annex 9, Table A9.1) than the older SRs with MAs (Naude et al, 2014; Fan et al, 2016; Meng et al, 2017; Snorgaard et al, 2017). All, except one, of the studies in the older SRs with MAs were included in the 4 prioritised SRs with MAs.

4.50 The NMA (Schwingshackl et al, 2018) was also not considered further because 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.

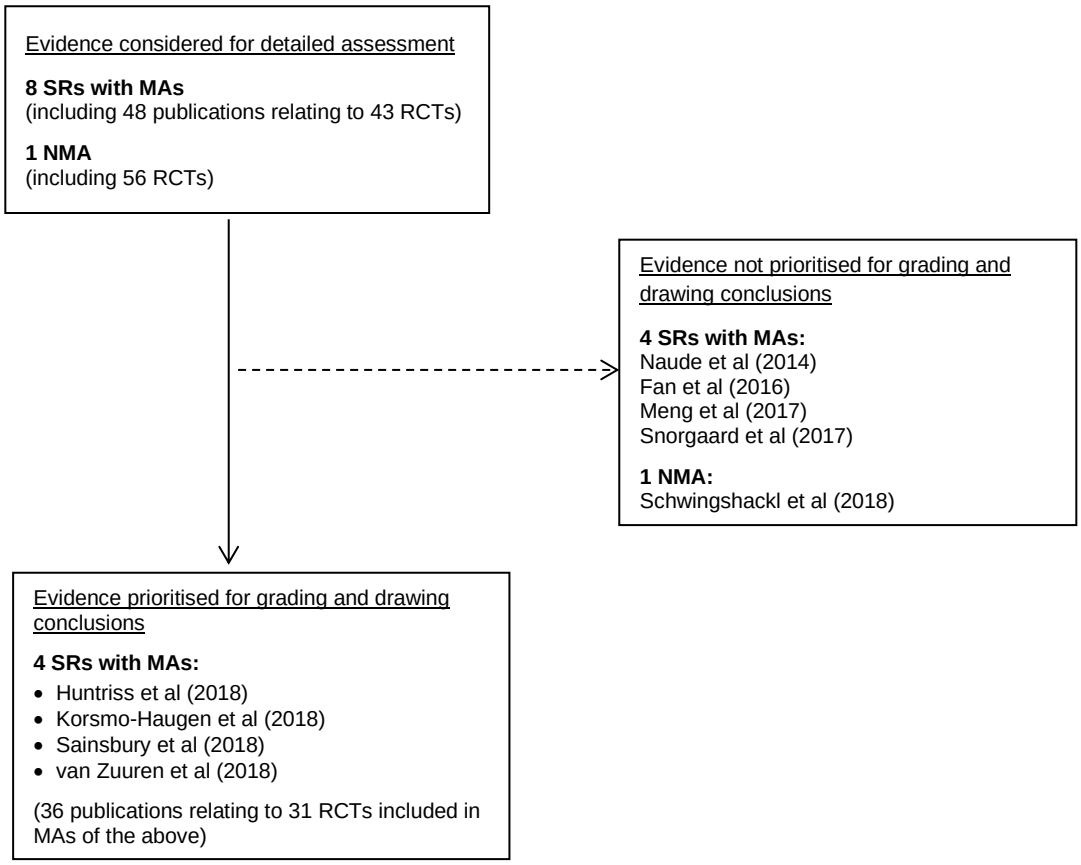
4.51 Summaries of the 4 non-prioritised SRs (Naude et al, 2014; Fan et al, 2016; Meng et al, 2017; Snorgaard et al, 2017) and the NMA (Schwingshackl et al, 2018) and their limitations is provided in Annex 10.

4.52 In total 31 primary RCTs (reported in 36 publications) were included in the MAs of the 4 prioritised SRs with MAs. Four out of the 31 RCTs reported at different follow-up time points:

- Parker et al (2002) (3 months); Brinkworth et al (2004) (3 and 16 months)
- Samaha et al (2003) (6 months); Stern et al (2004) (12 months)
- Jonasson et al (2014) (6 months); Guldbrand et al (2012) (6,12 and 24 months)
- Tay et al (2014) (6 months); Tay et al (2015) (12 months); Tay et al (2018) (24 months).

4.53 A flow diagram summarising the evidence prioritisation process is provided in Figure 4.2 below.

Figure 4.2: Flow diagram of evidence prioritisation process (described in in paragraphs 4.23 to 4.24 and 4.49 to 4.52)



Grouping of the evidence by outcomes and study duration

4.54 All primary and secondary outcomes were considered according to study duration.

4.55 Data were grouped according to shorter-term (minimum duration of 3 months) and longer-term (minimum duration of 12 months) measurements.

4.56 Out of the 36 publications included in the MAs of the 4 prioritised SRs with MAs, 18 reported outcomes in the shorter term (minimum duration of 3 months) only and 18 reported outcomes in the longer term (minimum duration of 12 months).

4.57 Out of the 18 publications that reported in the shorter term (minimum duration, 3 months), only 2 reported outcomes beyond 6 months: 1 reported at 8 months and was included in MAs at 6 months (Sainsbury et al, 2018) and 1 reported at 9 months but was included in a MA at 12 months (Sainsbury et al, 2018).

4.58 Out of the 18 publications that reported in the longer term (minimum duration, 12 months), 10 also reported outcomes in the shorter-term (at 3 and/or 6 months) and 6 reported outcomes beyond 12 months (4 at 24 months; 2 at 48 months).

4.59 In this report:

- shorter term refers to studies or assessments that reported at ≥3 to 6 months (since all except 1 of the timepoints included in shorter-term studies or assessments did not extend beyond 6 months)
- longer term refers to studies that reported outcomes at ≥12 months.

Process for drafting report

4.60 Chapters of the report were initially drafted by the secretariat and provided the basis for the WG's considerations. The final text, conclusions and recommendations were considered and agreed by SACN.

4.61 The draft report was published for public consultation (see paragraph 4.10) and comments received from interested parties were taken into consideration before the report was finalised. The main changes made to the draft report in response to the public consultation are summarised in Annex 11.

5 Assessment of the evidence

5.1 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 (see paragraph 4.49).

Overview of the prioritised SRs with MAs

5.2 The various markers and clinical outcomes of T2D considered in the 4 prioritised SRs with MAs are tabulated in Annex 12 (Table A12.1) and summarised in the overview below (see paragraphs 5.6 to 5.21). None of the 4 SRs with MAs considered total cholesterol:HDL cholesterol ratio. Only 1 (Huntriss et al, 2018) assessed change in medication use, specifically diabetes medication, as an outcome.

5.3 The main inclusion criteria for each of the 4 SRs with MAs are provided in Table 5.1 below.

Table 5.1: Main inclusion criteria for the prioritised SRs with MAs

SR	Carbohydrate comparison	Type of study and duration
Huntriss et al (2018)	No cut-off; must have reported lower carbohydrate intake than control group	RCTs (duration not specified) in adults aged ≥18 years with T2D
Korsmo-Haugen et al (2018)	Diet <40% TE vs diet >40% TE from carbohydrates	RCTs >3 months duration in adults with T2D Studies of adults with impaired glucose tolerance and/or T1D included if separate data provided for T2D individuals
Sainsbury et al (2018)	Diet ≤45% TE vs diet >45% TE from carbohydrates	RCTs ≥3 months duration in adults aged ≥18 years with T1D or T2D Crossover trials included if data from 1st phase, of at least 3 months, could be extracted Trials of adults with and without T2D included if ≥80% T2D or subgroup analysis conducted
van Zuuren et al (2018)	Diet ≤40% TE from carbohydrates vs low fat diet (≤30% TE from fats)	RCTs and controlled clinical trials ≥4 weeks duration in adults (aged ≥18 y) with T2D Crossover trials with washout ≥4 weeks. If ≤4 weeks, data only included if able to extract relevant data for 1st phase (before crossover)

5.4 In the overview below of the 4 SRs with MAs (paragraphs 5.6 to 5.21), the numeric ranges (where stated) used by the authors to define lower and higher carbohydrate diets (defined as %TE) are included in brackets. This is followed by classification of these intakes according to carbohydrate categories ('very low', 'low', 'moderate', 'high') (see paragraphs 2.21 to 2.22 and Table 2.1).

5.5 The overall risk of bias analyses for the primary RCTs included in the 4 SRs with MAs (as assessed by the authors) are also summarised. Further details of the individual risk of bias domains that were included for consideration and the criteria used to assess high, low and unclear risk of bias, are provided in Annex 13 (Tables A13.1 and A13.2).

Huntriss et al (2018)

5.6 Huntriss et al (2018) (18 RCTs, 2204 participants) compared the effects of a lower (not defined) compared to a higher (not defined) carbohydrate diet. RCTs were included if the lower carbohydrate group reported a lower carbohydrate intake than the higher carbohydrate group.

5.7 The primary outcome was HbA1c. Secondary outcomes were weight, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol, serum HDL cholesterol and diabetes medication use.

5.8 Meta-analyses were performed for change in each outcome at 12 months. No sensitivity or subgroup analyses were performed.

5.9 Risk of bias assessment: 15 out of the 18 studies were considered to be at high risk of bias in 1 or more of the 6 assessment criteria.

Korsmo-Haugen et al (2018)

5.10 Korsmo-Haugen et al (2018) (23 RCTs, 2178 participants) compared the effects of lower carbohydrate diets (defined as ≤40% TE; moderate) with higher carbohydrate diets (defined as >40% TE; moderate).

5.11 The outcomes considered were weight, HbA1c, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol. The authors did not distinguish between primary and secondary outcomes.

5.12 Meta-analyses were performed for change in each outcome for all studies combined and subgroup analyses were conducted based on study duration (3 to 6 months and ≥12 months). A sensitivity analysis was performed excluding studies at high risk of bias.

5.13 Risk of bias assessment: high risk, 10 studies; low risk, 3 studies; unclear risk, 10 studies.

Sainsbury et al (2018)

5.14 Sainsbury et al (2018)(25 RCTs, 2412 participants) compared the effects of lower carbohydrate diets (defined as ≤45% TE; moderate) with higher carbohydrate diets (defined as >45% TE; high).

5.15 The primary outcome was HbA1c. Secondary outcomes were weight, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol.

5.16 Meta-analyses were performed for weight change and HbA1c change at 3, 6, 12 and 24 months. All other outcomes were qualitatively evaluated. Subgroup analyses, based on prescribed quantity of carbohydrates ('low' and 'moderate' vs 'high') were performed at 3, 6 and 12 months. Sensitivity analyses were conducted (only for HbA1c) excluding studies at high risk of bias and studies with greater weight loss on the lower carbohydrate diet (to assess whether reductions in HbA1c were due to weight loss rather than reduction in carbohydrate intake).

5.17 Risk of bias assessment: high risk, 7 studies; low risk, 9 studies; unclear risk, 9 studies.

van Zuuren et al (2018)

5.18 van Zuuren et al (2018)(33 RCTs, 3 controlled clinical trials, 2161 participants) compared the effects of lower carbohydrate diets (defined as ≤40% TE; moderate) specifically with low fat diets (defined as ≤30% TE).

5.19 Primary outcomes were HbA1c, fasting plasma glucose, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol. Weight was a secondary outcome.

5.20 MAs were performed for change in each outcome at up to 8 weeks (not considered in this report), ≥8 to <16 weeks (not considered in this report), ≥16 to 26 weeks (approximately 4 to 6 months) and >26 weeks (all RCTs in this category were ≥12 months) and 2 years. Separate sensitivity analyses were performed for all outcomes using a fixed-effects model, excluding studies at high risk of bias and studies causing substantial heterogeneity.

5.21 Risk of bias assessment: high risk, 19 studies; low risk, 0 studies; unclear risk, 14 studies. Risk of bias assessed separately for 3 non-randomised trials: moderate risk, 1 study; serious risk, 2 studies.

Overview of primary data included in MAs of the prioritised SRs with MAs

5.22 In total, 31 primary RCTs (reported in 36 publications), were included in the MAs of the 4 SRs (9 out of the 36 publications related to 4 RCTs reporting at different follow-up time points (see paragraph 4.52).

5.23 Out of the 36 publications, 18 reported outcomes in the shorter term (≥3 to 6 months) only and 18 reported outcomes in the longer term (≥12 months) (see paragraphs 4.56 to 4.58).

Baseline characteristics of primary RCTs

5.24 Information on study and population characteristics from the primary data included in the MAs of the prioritised SRs is summarised below.

5.25 Baseline data on population characteristics (age, ethnicity, sex, sample size, BMI, duration since diabetes diagnosis), physical activity recommendations, dietary interventions and approach and dietary assessment are summarised for the 31 RCTs since these are applicable to all studies regardless of duration.

5.26 Details on loss to follow-up, medication and intakes of macronutrients and energy are described for the 36 publications to take account of study duration. These are reported separately for shorter-term (≥3 to 6 months) and longer-term (≥12 months) data.

Populations

5.27 Sample sizes of studies ranged from 24 to 419 participants (mean, n=100). Thirty out of 31 primary RCTs included both men and women; 1 included only women.

5.28 Out of 10 RCTs that reported ethnicity, the average proportion of White participants was 54.5% (range, 14 to 82%). Out of the 21 RCTs that did not report ethnicity, 1 was set in Japan while 20 were set in countries with predominantly White populations.

5.29 Twenty-five RCTs reported BMI of participants. The average BMI was 33 kg/m^2 (range, 25 to 43 kg/m^2) in the lower carbohydrate groups and 34 kg/m^2 (range, 27 to 43 kg/m^2) in the higher carbohydrate groups.

Duration since T2D diagnosis

5.30 The possibility of achieving T2D remission (or an effect of a dietary intervention) is greater with shorter compared to longer duration since T2D diagnosis (Steven et al, 2016). Out of 17 RCTs that reported T2D duration, participants were newly diagnosed in 2 RCTs. Average T2D duration in the remaining 15 RCTs was 9.1

years (range, 5.5 to 17.6 years) in the lower carbohydrate groups and 8.5 years (range, 6.2 to 16.2 years) in the higher carbohydrate groups. Fourteen RCTs did not report T2D duration.

Physical activity

5.31 Twenty RCTs included recommendations for physical activity. All participants received the same advice and reported time spent in physical activity did not differ between groups. Eleven RCTs did not provide any advice on physical activity.

Dietary interventions and approach

5.32 Details of the intervention approach (for example, number of sessions, motivational advice, group or individual discussions) were reported in 25 RCTs. Out of these, 15 provided one-to-one sessions, 7 provided group sessions and 3 provided a mixture of one-to-one and group sessions. The approach in all 25 RCTs was the same in the lower and higher carbohydrate groups. Six RCTs did not report details of the intervention approach.

5.33 Dietary advice varied between studies and included provision of meal plans and recipes, general healthy eating advice and recommendations to avoid, replace or increase particular nutrients or foods. Four RCTs provided participants with key foods that contributed 16 to 60% TE.

5.34 Few RCTs provided comprehensive dietary advice on carbohydrate type: 1 promoted wholegrain carbohydrates; 1 encouraged elimination of simple sugars and prescribed ‘complex carbohydrates’; 1 recommended avoidance of ‘processed carbohydrates – such as bread and pasta’; 2 prescribed fibre in both diet groups; 1 emphasised fruits and vegetables; and 9 promoted low-GI foods.

Assessment of dietary intakes

5.35 Dietary intakes were self-reported in 27 RCTs using a variety of dietary assessment methods: food diaries (17 RCTs), 24-hour recall (4 RCTs), food frequency questionnaire (1 RCT), weighed food records (3 RCTs) and a mixture of methods (2 RCTs). Four RCTs did not report dietary assessment method.

Loss to follow-up

5.36 Out of 36 publications, 34 reported the number of participants lost to follow-up.

5.37 Out of the 18 publications reporting shorter-term outcomes (≥3 to 6 months) 17 reported on loss to follow-up. Average loss to follow-up was 19.2% (range, 0 to 56%) in the lower carbohydrate group and 16.6% (range, 0 to 54%) in the higher carbohydrate group. One RCT did not report separately for each group (8% of all participants lost to follow-up).

5.38 Out of the 18 publications reporting longer-term outcomes (≥12 months), 17 reported on loss to follow-up. Average loss to follow-up was 27% (range, 0 to 46%) in the lower carbohydrate group and 26% (range, 0 to 51%) in the higher carbohydrate group.

Medication use

5.39 Details of medication use are provided in Annex 14 (Table A14.1). Medications taken by participants included: insulin; oral hypoglycaemic drugs; lipid-lowering drugs; anticoagulants; and blood pressure lowering drugs.

5.40 Ten out of the 31 RCTs specified diabetes medication in the inclusion or exclusion criteria. Out of these: 5 excluded individuals on insulin but allowed oral hypoglycaemic drugs, 1 excluded those on insulin or oral hypoglycaemic medication, 1 excluded those on insulin or >3 hypoglycaemic medications; 1 stipulated no use of anti-hyperglycaemic medications but did not specify if this included insulin; and 2 included only newly-diagnosed T2D individuals who were not being treated with any diabetes medication.

5.41 Twenty-nine out of the 36 publications reported changes in medication use: 12 provided descriptive analyses and 17 provided statistical analyses (11 between groups; 2 within group; 4 within and between groups).

5.42 Out of the 18 shorter-term (≥3 to 6 months) studies, 16 reported changes in medication use: 7 provided descriptive analyses and 9 provided statistical analyses (2 between and within groups; 5 between groups; 2 within groups). Out of the 7 between group statistical analyses, 3 reported no difference in medication change between the lower and higher carbohydrate groups and 4 reported a significantly greater reduction in medication in the lower compared to higher carbohydrate groups. Out of the 4 studies that assessed within group changes, 1 reported significant reductions in medication use in both groups and 3 reported a significant reduction in the lower carbohydrate group only.

5.43 Out of the 18 longer-term (≥12 months) studies, 13 reported changes in medication use: 5 provided descriptive analyses and 8 provided statistical analyses (2 between and within groups; 6 between groups). Out of the 8 between group statistical analyses, 4 reported no difference in medication change between lower and higher carbohydrate groups and 4 reported a significantly greater reduction in medication in the lower compared to higher carbohydrate groups. Out of the 2 within group analyses, 1 reported significant reductions in medication use in both groups and 1 reported no change in either group.

Macronutrient and energy intakes

5.44 Estimated intakes of carbohydrates, fats (total, SFA, PUFA, MUFA), protein and energy, reported in the primary data included in the MAs of the 4 SRs with MAs, are summarised in Table 5.2.

5.45 Estimated intake data (median and range of mean intakes) are reported for the 36 publications to take account of study duration and are grouped according to shorter-term (≥3 to 6 months) and longer-term (≥12 months) studies.

Carbohydrate intakes

Prescribed carbohydrate intakes

5.46 Prescribed intakes in the primary RCTs ranged between 14 and 50% TE (median, 40% TE) in the lower carbohydrate groups and 23 to 65% TE (median, 55% TE) in the higher carbohydrate groups. According to categories of carbohydrate intakes (see Table 2.1), prescribed intakes ranged from 'low' to 'high' in both lower and higher carbohydrate groups.

Reported carbohydrate intakes

5.47 Reported carbohydrate intakes are presented as % TE and g/day in Table 5.2. Where publications reported carbohydrate intakes in g/day, they were converted to the corresponding value as %TE (or vice versa if data on total energy intake was provided).

5.48 Thirty out of 36 publications reported mean carbohydrate intakes. According to categories of carbohydrate intakes, only 4 out of 30 publications compared 'low' vs 'high' when expressed as % TE. However, when expressed in g/day, none compared 'low' vs 'high' carbohydrate intakes. Most comparisons (% TE) were between 'moderate' and 'high' (16 publications) carbohydrate intakes (see Figure 5.1). Out of the remaining 10 publications, comparisons were between 'low' vs 'moderate' (4), 'moderate' vs 'moderate' (3) and 'high' vs 'high' (3) carbohydrate intakes. There was also considerable overlap in reported mean carbohydrate intakes between the lower and higher carbohydrate groups across studies.

5.49 In shorter-term (≥3 to 6 months) studies, reported mean carbohydrate intakes ranged from 13 to 47% TE or 49 to 218 g/day in the lower carbohydrate groups and 41 to 55% TE or 139 to 245 g/day in the higher carbohydrate groups. According to categories of carbohydrate intakes, reported mean intakes expressed as % TE ranged from 'low' to 'high' in the lower carbohydrate groups and 'moderate' to 'high' in the higher carbohydrate groups. When expressed as g/day, carbohydrate categories ranged from 'very low' to 'moderate' in the lower carbohydrate groups but remained 'moderate' to 'high' in the higher carbohydrate groups.

5.50 In longer-term (≥12 months) studies, reported mean carbohydrate intakes ranged from 17 to 46% TE or 74 to 233 g/day in the lower carbohydrate groups and 43 to 54% TE or 156 to 250 g/day in the higher carbohydrate groups. According to categories of carbohydrate intakes, reported mean intakes expressed as % TE or as g/day ranged from 'low' to 'high' in the lower carbohydrate groups and 'moderate' to 'high' in the higher carbohydrate groups.

5.51 The ranges and categories of carbohydrate intakes in the primary RCTs included in the MAs of each of the 4 SRs is presented in Table 5.3. In all 4, most comparisons between lower and higher carbohydrate groups by categories of reported carbohydrate intake were between 'moderate' vs 'high'.

Fat intakes

5.52 Reported mean intakes (% TE) of total fats, SFAs, PUFAs and MUFAs were greater in the lower compared to the higher carbohydrate groups in the shorter (≥3 to 6 months) and longer term (≥12 months).

5.53 In shorter-term (≥3 to 6 months) studies, reported mean intakes of:

- total fat ranged from 18 to 59% TE in the lower carbohydrate groups and 23 to 36% TE in the higher carbohydrate groups
- SFA ranged from 6 to 20% TE in the lower carbohydrate groups and 8 to 12% TE in the higher carbohydrate groups.
- PUFA ranged from 4 to 12% TE in the lower carbohydrate groups and 4 to 7% TE in the higher carbohydrate groups.
- MUFA ranged from 8 to 30% TE in the lower carbohydrate groups and 10 to 12% TE in the higher carbohydrate groups.

5.54 In longer-term (≥12 months) studies, reported mean intakes of:

- total fat ranged from 31 to 58% TE in the lower carbohydrate groups and 26 to 40% TE in the higher carbohydrate groups
- SFA ranged from 10 to 19% TE in the lower carbohydrate groups and 8 to 13% TE in the higher carbohydrate groups
- PUFA ranged from 6 to 13% TE in the lower carbohydrate groups and 4 to 7% TE in the higher carbohydrate groups
- MUFA ranged from 13 to 29% TE in the lower carbohydrate groups and 11 to 13% TE in the higher carbohydrate groups.

Protein intakes

5.55 Reported mean protein intakes were greater in the lower compared to the higher carbohydrate groups in the shorter (≥3 to 6 months) and longer term (≥12 months).

5.56 In shorter-term (≥3 to 6 months) studies, reported mean protein intakes ranged from 19 to 37% TE in the lower carbohydrate groups and 16 to 23% TE in the higher carbohydrate groups.

5.57 In longer-term (≥12 months) studies, reported mean protein intakes ranged from 16 to 27% TE in the lower carbohydrate groups and 16 to 21% TE in the higher carbohydrate groups.

Energy intakes

5.58 Out of the 31 RCTs reported in the 36 publications, 24 prescribed energy (calorie) restriction in at least one group. Prescribed energy restriction in the lower and higher carbohydrate groups was the same in 16 RCTs and differed in 8 RCTs (of those, 6 prescribed a minimum 500 kcal (2092 kJ) deficit only for the higher carbohydrate group).

5.59 Reported mean energy intakes were similar in the lower and higher carbohydrate groups in shorter- and longer-term studies. They were higher in longer-term than shorter-term studies for both groups (see Table 5.2).

5.60 In shorter-term (≥3 to 6 months) studies, reported mean energy intakes ranged from 1273 to 2029 kcal/day (5326 to 8489 kJ/day) (median, 1563 kcal/day; 6540 kJ/day) in the lower carbohydrate groups and 1197 to 1785 kcal/day (5008 to 7468 kJ/day) (median, 1544 kcal/day; 6460 kJ/day) in the higher carbohydrate groups.

5.61 In longer-term (≥12 months) studies, reported mean energy intakes ranged from 1251 to 2222 kcal/day (5234 to 9297 kJ/day) (median, 1707 kcal/day; 7,142 kJ/day) in the lower carbohydrate groups and 1420 to 2222 kcal/day (6104 to 9297 kJ/day) (median, 1757 kcal/day; 7351 kJ/day) in the higher carbohydrate groups.

Table 5.2: Reported macronutrient and energy intakes in the primary publications (n=36) included in MAs of 4 SRs

Macronutrient / energy	Duration (number of publications reporting)	Reported mean intakes Median (range)	
		Lower carbohydrate groups	Higher carbohydrate groups
Carbohydrate (% TE) [category]	Shorter term (15)	37 (13 to 47) [low to high]	50 (41 to 55) [moderate to high]
	Longer term (15)	39 (17 to 46) [low to high]	48 (43 to 54) [moderate to high]
Carbohydrate (g/day) [category]	Shorter term (14)	127 (49 to 218) [very low to moderate]	198 (139 to 245) [moderate to high]
	Longer term (14)	151 (74 to 233) [low to high]	213 (156 to 250) [moderate to high]
Fats (% TE)	Shorter term		
Total	(15)	40 (18 to 59)	29 (23 to 36)
SFA	(9)	10 (6 to 20)	8 (8 to 12)
PUFA	(7)	6 (4 to 12)	5 (4 to 7)
MUFA	(7)	17 (8 to 30)	11 (10 to 12)
	Longer term		
Total	(13)	44 (31 to 58)	31 (26 to 40)
SFA	(12)	12 (10 to 19)	10 (8 to 13)
PUFA	(8, 7)*	8 (6 to 13)	5 (4 to 7)
MUFA	(9, 8)*	16 (13 to 29)	11 (11 to 13)
Protein (% TE)	Shorter term (15)	26 (19 to 37)	19 (16 to 23)
	Longer term (12)	23 (16 to 27)	19 (16 to 21)
Energy (kcal/day; kJ/day)	Shorter term (14)	1557 (1273 to 2029) 6512 (5326 to 8489)	1549 (1197 to 1785) 6479 (5008 to 7468)
	Longer term (14)	1708 (1251 to 2222) 7144 (5234 to 9297)	1747 (1420 to 2222) 7309 (5941 to 9297)

*Number of publications reporting PUFA and MUFA intakes in lower and higher carbohydrate groups, respectively.

Table 5.3: Prescribed and reported carbohydrate intakes in primary publications included in MAs of 4 prioritised SRs

First author (year) (number of publications)	Prescribed carbohydrate intakes (% TE) median (range) [category]*		Reported mean carbohydrate intakes (% TE) median (range) [category]		Comparison of reported carbohydrate intakes by category (number of publications)
	Lower carbohydrate groups	Higher carbohydrate groups	Lower carbohydrate groups	Higher carbohydrate groups	
Huntriss (2018) (7)	30 (14 to 50) [low to high]	55 (53 to 58) [high to high]	31 (13 to 44) [low to moderate]	49 (43 to 52) [moderate to high]	low vs moderate (2) low vs high (1) moderate vs high (4)
Korsmo-Haugen (2018) (18)	40 (20 to 40) [low to moderate]	55 (23** to 60) [low to high]	39 (13 to 46) [low to high]	48 (43 to 52) [moderate to high]	low vs moderate (2) low vs high (1) moderate vs moderate (3) moderate vs high (9) high vs high (1) not reported (2)
Sainsbury (2018) (22)	40 (14 to 45) [low to moderate]	55 (23** to 60) [low to high]	38 (13 to 47) [low to high]	50 (41 to 55) [moderate to high]	low vs moderate (2) low vs high (1) moderate vs moderate (3) moderate vs high (11) high vs high (3) not reported (2)
van Zuuren (2018) (12)	28 (14 to 40) [low to moderate]	54 (23** to 60) [low to high]	33 (14 to 42) [low to moderate]	50 (45 to 52) [moderate to high]	low vs high (2) moderate vs moderate (1) moderate vs high (6) not reported (3)

* Relates to data from 31 RCTs.

**1 publication (Wolever et al, 2008) prescribed carbohydrate intakes between 20 to 25% TE in higher carbohydrate group. Exclusion of this study would have no effect on median prescribed carbohydrate intakes but ranges would change as follows: Korsmo-Haugen (2018), 50 to 65 [high to high]; Sainsbury (2018), 48 to 60 [high to high]; van Zuuren (2018), 50 to 60 [high to high].

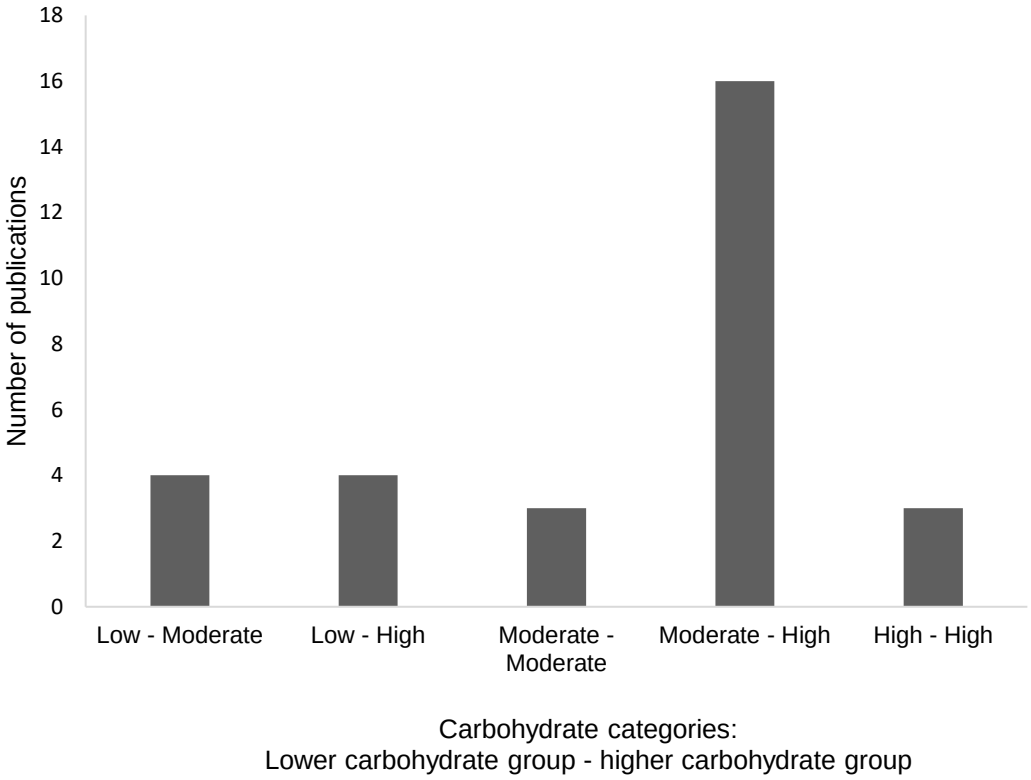


Figure 5.1: Comparisons of reported carbohydrate intakes (% TE) in the lower and higher carbohydrate groups in the primary publications according to categories of carbohydrate intake (results for 30 publications; 6 did not report intakes)

General limitations in the evidence base

5.62 An important limitation of the evidence considered was that the 4 SRs with MAs had different inclusion criteria for cut-offs used to define lower carbohydrate diets:

- <40% TE (Korsmo-Haugen et al, 2018; van Zuuren et al, 2018)
- <45% TE (Sainsbury et al, 2018)
- no cut-off; low carbohydrate diet as stated by author; to be included, the low carbohydrate group must have reported a lower carbohydrate intake than the control group (Huntriss et al, 2018).

5.63 In addition, van Zuuren et al (2018) only included RCTs if they compared lower carbohydrate diets specifically with low fat diets (defined as ≤30% TE from fats).

5.64 Several other limitations were identified in the evidence base and were considered as part of the assessment. These are summarised below.

Dietary approach and assessment

5.65 The studies considered were very heterogeneous in terms of the prescribed diets (amounts and types of carbohydrates, fats and proteins) and in the nutrition advice given to participants (approach and intensity of contact sessions).

5.66 The majority of primary RCTs were of dietary advice rather than feeding studies so adherence may have been challenging.

5.67 Although the majority of primary RCTs provided information on dietary intakes, the reliability of consumption estimates is uncertain since participants were not blinded to the intervention and dietary assessments were self-reported (using methods such as 24-hour recall, food diaries or food frequency questionnaires). Misreporting of food consumption and general under-reporting (by failing to report foods or drinks consumed and/or under-estimating quantities) is a known problem in dietary surveys (Bates, 2014). It is not known if misreporting differed systematically by dietary intervention group.

5.68 Technical difficulties in the dietary assessment process, such as assumptions made in relation to food composition, recipes and portion sizes, quality and completeness of food and nutrient databases, can also affect the accuracy of consumption estimates.

Carbohydrate intakes

5.69 There is no standard definition of a low carbohydrate diet and included studies used variable and wide-ranging definitions. According to categories of carbohydrate intake, a ‘low’ carbohydrate diet is defined as a carbohydrate intake of <130 g/day or <26% TE (based on an energy intake of 2,000 kcal/day). However, cut-offs for prescribed lower carbohydrate diets in the primary RCTs included in the prioritised SRs with MAs included carbohydrate intakes of up to 50% TE (range, 14 to 50% TE).

5.70 Reported mean carbohydrate intakes in the lower carbohydrate groups overlapped with those in the higher carbohydrate groups (see Table 5.2): shorter term (≥3 to 6 months), 13 to 47% TE in lower and 41 to 55% in higher carbohydrate groups; longer term (≥12 months), 17 to 46% TE in lower and 43 to 54% in higher carbohydrate groups.

5.71 Categories of carbohydrate intakes (‘very low’, ‘low’, ‘moderate’ or ‘high’) can be defined either in absolute amounts (g/day) or as percentage of TE (based on an energy intake of 2,000 kcal/day). In some primary studies that included an energy restricted diet, carbohydrate intakes in the lower carbohydrate group were prescribed in grams per day and categorised as ‘low’ when based on absolute amounts; however, since energy intakes were restricted, the relative amounts of

carbohydrates consumed would be higher and categorised as ‘moderate’ if expressed as percentage of TE.

5.72 Out of the 30 publications that reported mean carbohydrate intakes, only 4 compared ‘low’ vs ‘high’ intakes. Most comparisons (16 publications) were between ‘moderate’ vs ‘high’.

5.73 Studies did not consider types of carbohydrate (for example, wholegrain, refined grain, free sugars, fibre) being consumed in either dietary group or how this could affect the markers under consideration. Considerations were generally restricted to nutrients rather than foods, food patterns or the food matrix.

5.74 In order to compensate for reduced carbohydrate intake in the lower carbohydrate groups, the proportions of other macronutrients were increased. However, the potential impact of increasing the proportions of other macronutrients, or the type of macronutrient (for example, saturated or unsaturated fats; plant-based or animal-based proteins) on markers and clinical outcomes of T2D was generally not considered.

5.75 There was limited information on adherence to prescribed diets throughout the full duration of studies or consideration of how adherence might impact outcomes.

5.76 Lower carbohydrate diets were compared to a wide variety of higher carbohydrate diets including low fat, high or low GI, Mediterranean dietary pattern and standard diabetes care. The composition of these diets was very different in terms of the proportions of macronutrients making comparisons more difficult. The variety of comparator diets also made it difficult to compare the lower carbohydrate diets to current UK dietary recommendations for carbohydrate (as specified in the terms of reference).

Medication use

5.77 Reporting and measurement of medication use (oral hypoglycaemic drugs, insulin, anti-hypertensive and lipid-lowering drugs) and/or medication change was inconsistent and very variable. Some studies only included participants who were not on any diabetes medication or who were taking only oral glucose lowering drugs (no insulin). Several studies detailed medication use at the start of the study but did not report on this at follow-up. In other studies, adjustments to medication were made proactively at the start of the study and/or reactively during the study to minimise risk of hypoglycaemia. Many of the studies that reported changes in medication use provided descriptive rather than statistical analyses.

5.78 Medication change is an important potential confounder in these studies. For example, if diabetes medication was reduced or stopped (to reduce the risk of hypoglycaemia) in the lower carbohydrate group, this could underestimate any potential beneficial effect of the lower carbohydrate diet on HbA1c because the

dietary component would be acting alone without the added effect of the medication. In relation to blood lipids, any impact of dietary intervention may have been affected by pharmaceutical treatment (such as statins) to lower lipids.

Other issues

5.79 The independent effect of weight change on the other outcomes (HbA1c and blood lipids) is an important confounder. It is difficult to separate the effect of weight change on these markers and any observed benefits could be due to weight loss rather than a change in carbohydrate intakes.

5.80 Primary studies varied in the type of analysis (ITT or PP) used to compare lower and higher carbohydrate groups. ITT analysis includes all participants originally allocated at randomisation; it measures the effectiveness of an intervention and is more relevant to public health. PP analysis includes only those participants who completed the study; it measures the efficacy of an intervention and, since it only includes data on completers, it could over-estimate the effects of the diets. Although both types of analyses provide useful information, they answer different questions and should therefore be considered separately. However, all the MAs combined results of individual studies regardless of the type of analysis used.

5.81 Risk of bias was high or unclear in most of the primary RCTs included in the MAs. This reduces the confidence that can be placed on the estimates of the effects of lower carbohydrate diets on the markers of T2D and clinical outcomes under consideration.

5.82 Most shorter-term studies did not assess outcomes beyond 6 months and few longer-term studies assessed outcomes beyond 12 months.

5.83 The majority of participants in the primary RCTs were living with overweight (BMI ≥25 to <30 kg/m2) or obesity (BMI ≥30 kg/m2). It is not known if reported effects can be generalised to adults with a healthy weight (BMI ≥18.5 to <25 kg/m2).

5.84 Most RCTs did not report ethnicity and most were conducted in countries with predominantly White populations. Out of the studies that reported ethnicity of participants, none performed subgroup analyses based on ethnicity. Therefore, it is not known whether the effects of lower carbohydrate diets differ in individuals of different ethnicities with T2D.

Results of MAs in prioritised SRs with MAs and evidence grading

5.85 The focus of this evidence review was to compare between group differences in change from baseline for each outcome, since this presents the strongest evidence respecting the randomisation. These findings were used to grade the evidence.

5.86 All MAs from the 4 SRs reported results for the weighted mean difference (WMD) between the lower and higher carbohydrate diet groups in change from baseline for all the outcomes reported below. In all cases, the difference was reported as the change in the lower carbohydrate group minus change in the higher carbohydrate group. Detailed results for all outcomes are provided in Annex 15 (Tables A15.1 to A15.7).

5.87 The criteria used to grade the evidence are provided in chapter 4 (paragraphs 4.43 to 4.48 and Table 4.1). Summary tables of the evidence grading process for all outcomes, except medication use (since a MA was not conducted for this outcome; see paragraphs 5.206 to 5.210), are provided in Annex 16 (Tables A16.1A to A16.7B).

5.88 The results of within group changes in the lower and higher carbohydrate groups for the primary RCTs included in the MAs are provided for information in Annex 17 (Table A17.1 to A17.8) but were not used to grade the evidence. They are included to indicate the direction of effect and the absolute changes over time. The within group changes indicate that both interventions result in improved outcomes.

Body weight

5.89 All 4 SRs (Huntriss et al, 2018; Korsmo-Haugen et al, 2018; Sainsbury et al, 2018; van Zuuren et al, 2018) performed MAs on change in body weight.

Shorter-term data (≥3 to 6 months)

5.90 In total, 23 primary RCTs were included in the MAs of shorter-term (≥3 to 6 months) data.

5.91 Sainsbury et al (2018) conducted separate MAs for weight change at 3 and 6 months. MAs conducted by Korsmo-Haugen et al (2018) and van Zuuren et al (2018) included all measurements between 3 and 6 months together. Huntriss et al (2018) did not perform a MA of shorter-term (≥3 to 6 months) data but provided separate descriptive analyses at 3 and 6 months.

5.92 Sainsbury et al (2018), 3 months: significantly greater weight loss with the lower compared to the higher carbohydrate diet (WMD -1.08 kg, 95% CI -1.93 to -0.23, p=0.01, I^2=69%, random-effects model; 12 RCTs, 791 participants).

5.93 Subgroup analyses by prescribed carbohydrate quantity ('low' vs 'high' and 'moderate' vs 'high') reported significantly greater weight loss with the 'low' compared to the 'high' carbohydrate diet (WMD -2.47 kg, 95% CI -3.33 to -1.60, p<0.00001, I^2=0%, random-effects model; 4 RCTs, 268 participants) but no difference between the 'moderate' and 'high' carbohydrate diets (WMD 0.14 kg, 95% CI -0.30 to 0.59, p=0.53, I^2=0%, random-effects model; 8 RCTs, 523 participants).

5.94 Sainsbury et al, 6 months: no difference in weight loss between lower and higher carbohydrate diets (WMD -0.14 kg, 95% CI -0.94 to 0.65, p=0.72, I^2=48%, random-effects model; 9 RCTs, 953 participants). The MA included 1 RCT (contributing 11.7% weight in MA) of T1D participants only.

5.95 Subgroup analyses by prescribed carbohydrate quantity ('low' vs 'high' and 'moderate' vs 'high') reported no difference in weight loss with the 'low' compared to the 'high' carbohydrate diet (WMD -1.07 kg, 95% CI -2.52 to 0.37, p=0.14, I^2=33%, random-effects model; 4 RCTs, 240 participants) or between the 'moderate' and 'high' carbohydrate diets (WMD 0.29 kg, 95% CI -0.60 to 1.17, p=0.52, I^2=48%, random-effects model; 5 RCTs, 713 participants).

5.96 van Zuuren et al (2018): no difference in weight loss between lower and higher carbohydrate diets (WMD -2.51 kg, 95% CI -5.42 to 0.40, p=0.09, I^2=88%, random-effects model; 7 RCTs, 537 participants).

5.97 A sensitivity analysis excluding studies at high risk of bias was in agreement with the main analysis, reporting no difference in weight loss between lower and higher carbohydrate diets (WMD –1.69 kg, 95% CI -4.57 to 1.18, p=0.25, I^2=88%, random-effects model; 6 RCTs, 506 participants). A sensitivity analysis excluding studies causing substantial heterogeneity also reported no difference in weight loss between lower and higher carbohydrate diets (WMD 0.52 kg, 95% CI -0.28 to 1.33, p=0.2, I^2=0%, random-effects model; 5 RCTs, 417 participants).

5.98 Korsmo-Haugen et al (2018): no difference in weight loss between lower and higher carbohydrate diets (WMD -0.87 kg, 95% CI -1.88 to 0.15, p=NR, I^2=33%, random-effects model; 7 RCTs, 424 participants).

5.99 Huntriss et al (2018), 3 months: 3 out of 5 RCTs reported a significant difference in weight change in favour of the lower carbohydrate diet and 2 reported no difference between groups.

5.100 Huntriss et al (2018), 6 months: 4 out of 8 RCTs reported a significant difference in weight change in favour of the lower carbohydrate diet and 4 reported no difference between groups.

Summary: body weight, shorter term (≥3 to 6 months)

5.101 At 3 and 6 months, the largest MA was Sainsbury et al (2018) (12 RCTs, n=791 at 3 months; 9 RCTs, n=953 at 6 months).

5.102 At 3 months, there was significantly greater weight loss with the lower compared to the higher carbohydrate diet. This was in contrast with results of the MA at 6 months and the 2 other MAs (≥3 to 6 months) (Korsmo-Haugen et al, 2018; van Zuuren et al, 2018) that reported no difference in weight loss between groups.

5.103 The evidence was graded as **inconsistent** because of disagreement between results of the MA by Sainsbury et al (2018) at 3 months with the MA by Sainsbury et al (2018) at 6 months and the MAs by van Zuuren et al (2018) and Korsmo-Haugen et al (2018) at 3 to 6 months.

Longer-term data (≥12 months)

5.104 In total, 15 longer-term (≥12 months) primary RCTs were included in the MAs.

5.105 Sainsbury et al (2018): no difference in weight loss between lower and higher carbohydrate diets (WMD -0.43 kg, 95% CI -0.93 to 0.07, p=0.09, I^2=0%, random-effects model; 10 RCTs, 1267 participants). A subgroup analysis based on prescribed carbohydrate quantity of the lower carbohydrate diet ('low' or 'moderate') reported no difference in weight change between a 'low' and 'high' carbohydrate diet (WMD 0.58 kg, 95% CI -0.83 to 1.99, p=0.42, I^2=0%, random-effects model; 3 RCTs, 244 participants) but a significantly greater weight loss with 'moderate' compared to a 'high' carbohydrate diet (WMD -0.58 kg, 95% CI -1.11 to -0.04, p=0.04, I^2=0%, random-effects model; 7 RCTs, 1023 participants).

5.106 Korsmo-Haugen et al (2018): no difference in weight change between lower and higher carbohydrate diets (WMD 0.14 kg, 95% CI -0.29 to 0.57, p=NR, I^2=0%, random-effects model; 10 RCTs, 1163 participants).

5.107 Huntriss et al (2018): no difference in weight change between lower and higher carbohydrate diets (WMD 0.28 kg, 95% CI -1.37 to 1.92, p=0.74, I^2=75%, random-effects model; 6 RCTs, 567 participants).

5.108 van Zuuren et al (2018): no difference in weight loss between lower and higher carbohydrate diets (WMD -0.19 kg, 95% CI -1.65 to 1.27, p=0.80, I^2=0%, random-effects model; 5 RCTs, 483 participants). Results using a fixed-effects model agreed with those of the random-effects model. Results of 2 sensitivity analyses (excluding RCTs at high risk of bias and RCTs causing substantial heterogeneity) agreed with the main results.

Summary: body weight, longer term (≥12 months)

5.109 The 2 largest MAs, Korsmo-Haugen et al (2018) (10 RCTs, n=1163) and Sainsbury et al (2018) (10 RCTs, n=1267), both reported no significant difference in weight loss between lower and higher carbohydrate diets in the longer term (≥12 months). These results agreed with those of the 2 other MAs (Huntriss et al, 2018; van Zuuren et al, 2018).

5.110 The evidence was graded as **adequate**.

Lower vs higher carbohydrate diets and body weight
Shorter term (≥3 to 6 months) • **Inconsistent** evidence Longer term (≥12 months) • No difference in effect • **Adequate** evidence

HbA1c

5.111 All 4 SRs performed MAs on the effect of a lower vs higher carbohydrate diet on HbA1c.

Shorter-term data (≥3 to 6 months)

5.112 In total, 22 primary RCTs were included in the MAs of shorter-term (≥3 to 6 months) data.

5.113 Sainsbury et al (2018) conducted separate MAs for HbA1c change at 3 and 6 months.

5.114 Huntriss et al (2018) did not perform a MA of shorter-term (≥3 to 6 months) data but provided separate descriptive analyses at 3 and 6 months.

5.115 Sainsbury et al (2018), 3 months: significantly greater reduction in HbA1c concentration with the lower compared to the higher carbohydrate diet (WMD -0.19% (-1.9 mmol/mol), 95% CI -0.33 to -0.05, p=0.008, I^2=28%, random-effects model; 12 RCTs, 791 participants).

5.116 Subgroup analyses by prescribed carbohydrate quantity ('low' vs 'high' and 'moderate' vs 'high') reported a significantly greater reduction in HbA1c with the 'low' compared to the 'high' carbohydrate diet (WMD -0.47% (-4.7 mmol/mol), 95% CI -0.71 to -0.23, p=0.0001, I^2=0%, random-effects model; 4 RCTs, 268 participants) but no significant difference between the 'moderate' and 'high' carbohydrate diets (WMD -0.06% (-0.6 mmol/mol), 95% CI -0.17 to 0.06, p=0.33, I^2=0%, random-effects model; 8 RCTs, 523 participants).

5.117 To assess the effect of weight loss on HbA1c change, a sensitivity analysis excluding RCTs with significantly greater weight loss on the lower carbohydrate diet reported that the difference between the lower and higher carbohydrate diets was no longer significant (WMD -0.05% (-0.5 mmol/mol), 95% CI -0.17 to 0.06, p=0.35, I^2=0%, random-effects model; 7 RCTs, 481 participants).

5.118 Results of a sensitivity analysis, removing RCTs at high risk of bias agreed with the results of the main analysis (WMD -0.25% (-2.5 mmol/mol), 95% CI -0.42 to -0.07, p=NR, I^2=NR, random-effects model; 8 RCTs, 552 participants).

5.119 Sainsbury et al (2018), 6 months: the MA included 1 RCT of T1D participants (Strychar et al, 2009). A sensitivity analysis excluding this study reported a significantly greater reduction in HbA1c with the lower compared to the higher carbohydrate diets (WMD -0.19% (-1.9 mmol/mol), 95% CI -0.35 to -0.02, p=NR, I^2=44%, random-effects model; 10 RCTs, 1054 participants).

5.120 A subgroup analysis by prescribed carbohydrate quantity reported a significantly greater reduction in HbA1c with a 'low' compared to a 'high' carbohydrate diet (WMD -0.36% (-3.6 mmol/mol), 95% CI -0.62 to -0.09, p=0.008, I^2=0, random-effects model; 5 RCTs, 295 participants) (results of a subgroup analysis for 'moderate' vs 'high' carbohydrate diet not reported here due to inclusion of study with T1D participants: Strychar et al, 2009).

5.121 A sensitivity analysis excluding RCTs at high risk of bias agreed with the main analysis (WMD -0.21% (-2.1 mmol/mol), 95% CI -0.38 to -0.05, p=NR, I^2=NR, random-effects model; 8 RCTs, 896 participants).

5.122 van Zuuren et al (2018): significantly greater reduction in HbA1c with the lower compared to the higher carbohydrate diet (WMD -0.26% (-2.6 mmol/mol), 95% CI -0.50 to -0.02, p=0.04, I^2=59%, random-effects model; 7 RCTs, 539 participants). Results of an analysis using a fixed-effects model agreed with those of the random-effects model (WMD -0.23% (-2.3 mmol/mol), 95% CI -0.38 to -0.09, p=0.001, I^2=59%, fixed-effects model; 7 RCTs, 539 participants). Results of a sensitivity analysis, excluding studies causing substantial heterogeneity agreed with the main results (WMD -0.42% (-4.2 mmol/mol), 95% CI -0.61 to -0.24, p<0.00001, I^2=0%, random-effects model; 5 RCTs, 310 participants). A sensitivity analysis excluding studies at high risk of bias showed no effect of the lower compared to higher carbohydrate diet on HbA1c change (WMD -0.20% (-2.0 mmol/mol), 95% CI -0.44 to 0.04, p=0.1, I^2=55%, random-effects model; 6 RCTs, 508 participants).

5.123 Korsmo-Haugen et al (2018): significantly greater reduction in HbA1c with the lower compared to higher carbohydrate diet (WMD -0.17% (-1.7 mmol/mol), 95% CI -0.27 to -0.08, p=NR, I^2= 0%; random-effects model; 6 RCTs, 395 participants).

5.124 Huntriss et al (2018), 3 months: 2 out of 7 RCTs reported a significant difference in favour of the lower carbohydrate group (p<0.05) but significance was lost (p=0.06) after adjusting results for baseline differences in HbA1c.

5.125 Huntriss et al (2018), 6 months: 4 out of 8 RCTs reported a significant difference between groups in favour of the lower carbohydrate diet; 1 study reported that significance was lost after taking account of differences in baseline HbA1c.

Summary: HbA1c, shorter term (≥3 to 6 months)

5.126 At 3 and 6 months, the largest MA was Sainsbury et al (2018) (12 RCTs, n=791 at 3 months; 10 RCTs, n=1054 at 6 months). At both time points there were significantly greater reductions in HbA1c with the lower compared to the higher carbohydrate diets. These results agreed with those of the 2 other MAs (Korsmo-Haugen et al, 2018; van Zuuren et al, 2018).

5.127 The evidence was graded as **adequate**.

Longer-term data (≥12 months)

5.128 In total, 16 longer-term (≥12 months) RCTs were included in the MAs.

5.129 Sainsbury et al (2018) conducted separate MAs for HbA1c change at 12 and 24 months. van Zuuren et al (2018) also conducted separate MAs at ≥12 and 24 months.

5.130 Sainsbury et al (2018), 12 months: no difference in HbA1c reduction between lower and higher carbohydrate diets (WMD -0.09% (-0.9 mmol/mol), 95% CI -0.21 to 0.03, p=0.12, I^2=16%, random-effects model; 12 RCTs, 1403 participants).

5.131 A subgroup analysis based on prescribed carbohydrate quantity reported no difference in HbA1c reduction between a 'low' and 'high' carbohydrate diet (WMD -0.17% (-1.7 mmol/mol), 95% CI -0.44 to 0.09, p=0.19, I^2=0%, random-effects model; 4 RCTs, 301 participants) or a 'moderate' and 'high' carbohydrate diet (WMD -0.08% (-0.8 mmol/mol), 95% CI -0.23 to 0.06, p=0.25, I^2=30%, random-effects model; 8 RCTs, 1102 participants).

5.132 A sensitivity analysis excluding RCTs at high risk of bias reported a significantly greater reduction in HbA1c in the lower compared to the higher carbohydrate diet (WMD -0.13% (-1.3 mmol/mol), 95% CI -0.26 to -0.01, p=NR, I^2=NR, random-effects model; 11 RCTs, 1438 participants) which disagreed with results of the main analysis.

5.133 Sainsbury et al (2018), 24 months: no difference in HbA1c reduction between lower and higher carbohydrate groups (WMD -0.11% (-1.1 mmol/mol), 95% CI -0.38 to 0.15, p=NR, I^2=NR, random-effects model; 3 RCTs, 526 participants).

5.134 Korsmo-Haugen et al (2018), ≥12 months: no difference in HbA1c reduction between lower and higher carbohydrate diets (WMD 0.00%, 95% CI -0.10 to 0.09, p=NR, I^2= 0%, random-effects model; 10 RCTs, 1030 participants).

5.135 Huntriss et al (2018), 12 months: significantly greater reduction in HbA1c in the lower compared to higher carbohydrate diets (WMD -0.28% (-2.8 mmol/mol), 95% CI -0.53 to -0.02, p=0.03, I^2=54%, random-effects model; 7 RCTs, 645 participants).

5.136 van Zuuren et al (2018), ≥12 months: significantly greater reduction in HbA1c with a lower compared to a higher carbohydrate diet (WMD -0.36% (-3.6 mmol/mol), 95% CI -0.58 to -0.14, p=0.001, I^2=0%, random-effects model; 4 RCTs, 390 participants). Results using a fixed-effects model agreed with results of the random-effects model. A sensitivity analysis, excluding studies at high risk of bias (1 RCT) reported no difference in HbA1c reduction between the lower and higher carbohydrate diets (WMD -0.25% (-2.5 mmol/mol), 95% CI -0.66 to 0.15, p=0.22, I^2=0%, random-effects model; 3 RCTs, 274 participants).

5.137 van Zuuren et al (2018), 24 months: no difference in HbA1c reduction between lower and higher carbohydrate diets (WMD -0.02% (-0.2 mmol/mol), 95% CI -0.37 to 0.41, p=0.93, I^2=13%, random-effects model; 3 RCTs, 199 participants). Results from analysis using a fixed-effects model agreed with those of the random-effects model.

Summary: HbA1c, longer term (≥12 months)

5.138 The largest MA (Sainsbury et al, 2018) (12 RCTs, n=1403) reported no difference in HbA1c reduction between the lower and higher carbohydrate diets in the longer term (≥12 months). These results agreed with those of the second largest MA (Korsmo-Haugen et al, 2018) (10 RCTs, n=1030) but disagreed with a sensitivity analysis (excluding 1 RCT at high risk of bias) by Sainsbury et al (2018) (11 RCTs, n=1438) and the 2 smaller MAs, Korsmo-Haugen et al, 2018 (7 RCTs, n=645) and van Zuuren et al, 2018 (4 RCTs, n=390).

5.139 The evidence was graded as **inconsistent** because of disagreement between results of the largest MA (Sainsbury et al, 2018) (12 RCTs, n=1403) with those of a sensitivity analysis (excluding 1 RCT at high risk of bias) (Sainsbury et al, 2018) and with the 2 other MAs (Huntriss et al, 2018; van Zuuren et al, 2018).

5.140 Two MAs reported HbA1c change at 24 months (Sainsbury et al, 2018; van Zuuren et a, 2018). The largest (Sainsbury et al, 2018) (3 RCTs, n=526) reported no difference in HbA1c change between the lower and higher carbohydrate diets. This agreed with results of the other MA (van Zuuren et al, 2018) (3 RCTs, n=199).

5.141 The evidence was graded as **adequate**.

Lower vs higher carbohydrate diets and HbA1c
Shorter term (≥3 to 6 months) • Greater HbA1c reduction in the lower carbohydrate group • **Adequate** evidence Longer term (≥12 to <24 months) • **Inconsistent** evidence Longer term (24 months) • No difference in effect • **Adequate** evidence

Fasting plasma glucose

5.142 One SR with MA (van Zuuren et al, 2018) assessed the difference in effect between lower and higher carbohydrate diets on fasting plasma glucose.

Shorter-term data (≥3 to 6 months)

5.143 In total, 6 RCTs were included in the MA of shorter-term (≥3 to 6 months) data.

5.144 van Zuuren et al (2018): significantly greater reduction in fasting plasma glucose with lower compared to higher carbohydrate diets (WMD -0.51 mmol/L, 95% CI -0.91 to -0.12, p=0.01, I^2=71%, random-effects model; 6 RCTs, including 1 non-randomised trial, 396 participants). Results of an analysis using a fixed-effects model agreed with those of the random-effects model (WMD -0.27 mmol/L, 95% CI -0.38 to -0.16, p<0.00001, I^2=71%, fixed-effects model; 6 RCTs, 396 participants).

5.145 A sensitivity analysis excluding RCTs at high risk of bias agreed with the main results, reporting a significantly greater reduction in fasting plasma glucose with the lower compared to the higher carbohydrate diet (WMD -0.41 mmol/L, 95% CI -0.78 to -0.03, p=0.03, I^2=67%, random-effects model; 5 RCTs, 365 participants). Results of a sensitivity analysis excluding RCTs causing substantial heterogeneity also agreed with the main results (WMD -0.76 mmol/L, 95% CI -1.05 to -0.47, p<0.00001, I^2=0%, random-effects model; 4 RCTs, 167 participants).

Summary: fasting plasma glucose, shorter term (≥3 to 6 months)

5.146 One MA (van Zuuren et al, 2018) (6 RCTs, n=396) reported a significantly greater reduction in fasting plasma glucose with lower compared to higher carbohydrate diets in the shorter term (≥3 to 6 months).

5.147 The evidence was graded as **moderate** because only 1 MA (n=396), which compared lower carbohydrate diets specifically with low fat (≤30% TE from fats) diets, assessed this outcome. The MA also included 1 non-randomised trial.

Longer-term data (≥12 months)

5.148 van Zuuren et al (2018) conducted separate MAs at ≥12 and 24 months. The results at 24 months were not considered because only 2 RCTs were included in the MA (see Table 4.1, chapter 4).

5.149 In total, 4 RCTs were included in the MA at ≥12 months.

5.150 van Zuuren et al (2018): no difference in fasting plasma glucose reduction between lower and higher carbohydrate diets (WMD -0.37 mmol/L, 95% CI -1.22 to 0.48, p=0.39, I^2=92%, random-effects model; 4 RCTs, 340 participants). Results of an analysis using a fixed-effects model disagreed with the results of the random-effects model (WMD -0.51 mmol/L, 95% CI -0.72 to -0.30, p<0.00001, I^2=92%, fixed-effects model; 4 RCTs, 340 participants).

5.151 A sensitivity analysis excluding studies at high risk of bias, reported no difference in effect between lower and higher carbohydrate diets (WMD -0.05 mmol/L, 95% CI -1.11 to 1.02, p=0.93, I^2=92%, random-effects model; 3 RCTs, 224 participants).

Summary: fasting plasma glucose, longer term (≥12 months)

5.152 One MA (van Zuuren et al, 2018) (4 RCTs, n=340) reported no difference in effect between lower and higher carbohydrate diets in reducing fasting plasma glucose in the longer term (≥12 months).

5.153 The evidence was graded as **insufficient** because heterogeneity was 92% in the only MA (n=340) that considered this outcome, reflecting a high degree of uncertainty in the value of the pooled estimate.

Lower vs higher carbohydrate diets and fasting plasma glucose
Shorter term (≥3 to 6 months) • Greater reduction in fasting plasma glucose in the lower carbohydrate group • **Moderate** evidence Longer term (≥12 months) • **Insufficient** evidence

Serum total cholesterol

5.154 Two SRs with MAs (Huntriss et al, 2018; Korsmo-Haugen et al, 2018) examined the difference in effect between lower and higher carbohydrate diets on serum total cholesterol.

Shorter-term data (≥3 to 6 months)

5.155 In total, 4 RCTs were included in the MA of shorter-term (≥3 to 6 months) data.

5.156 Huntriss et al (2018) did not conduct a MA or provide a descriptive analysis of shorter-term (≥3 to 6 months) data.

5.157 Korsmo-Haugen et al (2018): no difference between lower and higher carbohydrate diets on reducing total serum cholesterol (WMD -0.06 mmol/L, 95% CI -0.41 to 0.30, p=NR, I^2=57%, random-effects model; 4 RCTs, 279 participants).

Summary: serum total cholesterol, shorter term (≥3 to 6 months)

5.158 One MA (Korsmo-Haugen et al, 2018) (4 RCTs, n=279) reported no difference in effect between lower and higher carbohydrate diets on serum total cholesterol reduction in the shorter term (≥3 to 6 months).

5.159 The evidence was graded as **moderate** because there was only 1 MA with a small sample size (n=279).

Longer-term data (≥12 months)

5.160 In total, 13 longer-term (≥12 months) primary RCTs were included in the MAs.

5.161 Korsmo-Haugen et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum total cholesterol (WMD 0.07 mmol/L, 95% CI -0.04 to 0.19, p=NR, I^2=23%, random-effects model; 10 RCTs, 1094 participants).

5.162 Huntriss et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum total cholesterol (WMD -0.08 mmol/L, 95% CI -0.23 to 0.08, p=0.35, I^2=60%, random-effects model; 7 RCTs, 645 participants).

Summary: serum total cholesterol, longer term (≥12 months)

5.163 The largest MA (Korsmo-Haugen et al, 2018) (10 RCTs, n=1094) reported no difference in effect between lower and higher carbohydrate diets on change in serum total cholesterol in the longer term (≥12 months). This agreed with the results of the other MA (Huntriss et al, 2018) (7 RCTs, n=645).

5.164 The evidence was graded as **adequate**.

Lower vs higher carbohydrate diets and serum total cholesterol
Shorter term (≥3 to 6 months) • No difference in effect • **Moderate** evidence Longer term (≥12 months) • No difference in effect • **Adequate** evidence

Serum triacylglycerol

5.165 Three SRs with MAs (Huntriss et al, 2018; Korsmo-Haugen et al, 2018; van Zuuren et al, 2018) assessed the difference in effect between lower and higher carbohydrate diets on serum triacylglycerol.

Shorter-term data (≥3 to 6 months)

5.166 In total, 12 RCTs were included in MAs of shorter-term (≥3 to 6 months) data.

5.167 Huntriss et al (2018) did not conduct a MA or provide a descriptive analysis of shorter-term (≥3 to 6 months) data.

5.168 Korsmo-Haugen et al (2018): greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets but the upper confidence interval was 0 and significance was not reported (WMD -0.18 mmol/L, 95% CI -0.36 to 0.00, p=NR, I^2=20%, random-effects model; 7 RCTs, 424 participants).

5.169 van Zuuren et al (2018): significantly greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets (WMD -0.22 mmol/L, 95% CI -0.37 to

-0.08, p=0.002, I^2=41%, random-effects model; 6 RCTs, 508 participants). Results of analysis using a fixed-effects model agreed with those of the random-effects model (WMD -0.22 mmol/L, 95% CI -0.32 to -0.11, p<0.0001; I^2=41%, fixed-effects model; 6 RCTs, 508 participants).

Summary: serum triacylglycerol, shorter term (≥3 to 6 months)

5.170 The largest MA (van Zuuren et al, 2018) (6 RCTs, n=508) reported a significantly greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets in the shorter term (≥3 to 6 months). This was consistent with results of the other MA (Korsmo-Haugen et al, 2018) (7 RCTs, n=424) but significance was not reported (and upper confidence interval was 0).

5.171 The evidence was graded as **adequate**.

Longer-term data (≥12 months)

5.172 In total, 13 longer-term (≥12 months) RCTs were included in the MAs.

5.173 van Zuuren et al (2018) conducted separate MAs at ≥12 and 24 months. The results at 24 months were not considered because only 2 RCTs were included in the MA (see Table 4.1, chapter 4).

5.174 Korsmo-Haugen et al (2018): no difference in effect between lower and higher carbohydrate diets on reduction in serum triacylglycerol (WMD -0.10 mmol/L, 95% CI -0.23 to 0.03, p=NR; I^2=61%, random-effects model; 9 RCTs, 967 participants).

5.175 Huntriss et al (2018): significantly greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets (WMD -0.24 mmol/L, 95% CI -0.35 to -0.13, p<0.0001; I^2=0%, random-effects model; 7 RCTs, 645 participants).

5.176 van Zuuren et al (2018): significantly greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets (WMD -0.25 mmol/L, 95% CI -0.47 to -0.04, p=0.02; I^2=73%, random-effects model; 5 RCTs, 468 participants). Results of analysis using a fixed-effects model agreed with those of the random-effects model (WMD -0.25 mmol/L, 95% CI -0.36 to -0.15, p<0.00001; I^2=73%, fixed-effects model; 5 RCTs, 468 participants). Sensitivity analyses excluding studies at high risk of bias and studies causing substantial heterogeneity (same RCT excluded in both) reported a significantly greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets (WMD -0.14 mmol/L, 95% CI -0.26 to -0.02, p=0.02, I^2=0%, random-effects model; 4 RCTs, 352 participants).

Summary: serum triacylglycerol, longer term (≥12 months)

5.177 The largest MA (Korsmo-Haugen et al, 2018) (9 RCTs, n=967) reported no difference in effect between lower and higher carbohydrate diets on serum triacylglycerol reduction in the longer term (≥12 months). This was in contrast to results of the 2 other MAs (Huntriss et al, 2018; 7 RCTs, n=645) (van Zuuren et al,

2018; 5 RCTs, n=468) that reported a significantly greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets.

5.178 The evidence was graded as **inconsistent** because of disagreement between results of the largest MA (Korsmo-Haugen et al, 2018) (9 RCTs, n=967) and those of the 2 other MAs (Huntriss et al, 2018) (7 RCTs, n=645) (van Zuuren et al, 2018) (5 RCTs, n=468).

Lower vs higher carbohydrate diets and serum triacylglycerol
Shorter term (≥3 to 6 months) • Greater reduction in serum triacylglycerol in the lower carbohydrate group • **Adequate** evidence Longer term (≥12 months) • **Inconsistent** evidence

Serum LDL cholesterol

5.179 Three SRs with MAs (Huntriss et al, 2018; Korsmo-Haugen et al, 2018; van Zuuren et al, 2018) examined the difference in effect between lower and higher carbohydrate diets on serum LDL cholesterol.

Shorter-term data (≥3 to 6 months)

5.180 In total, 9 RCTs were included in MAs of shorter-term (≥3 to 6 months) data.

5.181 Huntriss et al (2018) did not conduct a MA of shorter-term (≥3 to 6 months) data.

5.182 Korsmo-Haugen et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol (WMD -0.08 mmol/L, 95% CI -0.29 to 0.14, p=NR, I^2=50%, random-effects model; 6 RCTs, 345 participants).

5.183 van Zuuren et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol (WMD 0.02 mmol/L 95% CI -0.09 to 0.13, p=0.75, I^2=0%, random-effects model; 5 RCTs, 372 participants). Results of analysis using a fixed-effects model were the same as those of the random-effects model.

Summary: serum LDL cholesterol, shorter term (≥3 to 6 months)

5.184 The largest MA (van Zuuren et al, 2018) (5 RCTs, n=372) reported no difference in effect between lower and higher carbohydrate diets on change in serum LDL

cholesterol in the shorter term (≥3 to 6 months). This agreed with results of the other MA (Korsmo-Haugen et al, 2018) (6 RCTs, n=345).

5.185 The evidence was graded as **adequate**.

Longer-term data (≥12 months)

5.186 In total, 11 longer-term (≥12 months) RCTs were included in the MAs.

5.187 Korsmo-Haugen et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol (WMD 0.03 mmol/L, 95% CI -0.10 to 0.16, p=NR, I^2=51%, random-effects model; 9 RCTs, 1064 participants).

5.188 Huntriss et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol (WMD 0.05 mmol/L, 95% CI -0.10 to 0.19, p=0.54, I^2=0%, random-effects model; 5 RCTs, 389 participants).

5.189 van Zuuren et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol (WMD -0.07 mmol/l, 95% CI -0.23 to 0.09, p=0.41, I^2=50%, random-effects model; 4 RCTs, 375 participants). Results of analysis using a fixed-effects model agreed with those of the random-effects model (WMD -0.08 mmol/L, 95% CI -0.20 to 0.03, p=0.15, I^2=50%, fixed-effects model; 4 RCTs, 375 participants). A sensitivity analysis excluding RCTs at high risk of bias (1 RCT) also reported no difference in effect between the lower and higher carbohydrate diets (WMD 0.00 mmol/L, 95% CI -0.14 to 0.15, p=0.95, I^2=0%, random-effects model; 3 RCTs, 259 participants).

Summary: serum LDL cholesterol, longer term (≥12 months)

5.190 The largest MA (Korsmo-Haugen et al, 2018) (9 RCTs, n=1064) reported no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol in the longer term (≥12 months). This agreed with results of the 2 other SRs with MAs (Huntriss et al, 2018; 5 RCTs, n=389) (van Zuuren et al, 2018; 4 RCTs, n=375).

5.191 The evidence was graded as **adequate**.

Lower vs higher carbohydrate diets and serum LDL cholesterol
Shorter term (≥3 to 6 months) • No difference in effect • **Adequate** evidence Longer term (≥12 months) • No difference in effect • **Adequate** evidence

Serum HDL cholesterol

5.192 Three SRs with MAs (Huntriss et al, 2018; Korsmo-Haugen et al, 2018; van Zuuren et al, 2018) assessed the difference in effect between lower and higher carbohydrate diets on HDL cholesterol.

Shorter-term data (≥3 to 6 months)

5.193 In total, 10 RCTs were included in the MAs of shorter-term (≥3 to 6 months) data.

5.194 Huntriss et al (2018) did not conduct a MA of shorter-term (≥3 to 6 months) data or provide descriptive analyses.

5.195 van Zuuren et al (2018): no difference in effect between lower and higher carbohydrate diets on increasing serum HDL cholesterol (WMD 0.09 mmol/L, 95% CI -0.03 to 0.22, p=0.13, I^2=91%, random-effects model; 6 RCTs, 508 participants). Results of analysis using a fixed-effects model agreed with those of the random-effects model (WMD -0.01 mmol/L, 95% CI -0.04 to 0.02, p=0.43, I^2=91%, fixed-effects model; 6 RCTs, 508 participants). A sensitivity analysis excluding studies causing substantial heterogeneity (2 RCTs) reported a significantly greater increase in serum HDL cholesterol with lower compared to higher carbohydrate diets (WMD 0.17 mmol/L, 95% CI 0.11 to 0.23, p<0.00001, I^2=0%, random-effects model; 4 RCTs, 283 participants).

5.196 Korsmo-Haugen et al (2018): no difference in effect between lower and higher carbohydrate diets on change in serum HDL cholesterol (WMD -0.01 mmol/L, 95% CI -0.07 to 0.04, p=NR, I^2=15%, random-effects model; 6 RCTs, 345 participants).

Summary: serum HDL cholesterol, shorter term (≥3 to 6 months)

5.197 The largest MA (van Zuuren et al, 2018) (6 RCTs, n=508) reported no difference in effect between the lower and higher carbohydrate diets on serum HDL cholesterol in the shorter term (≥3 to 6 months). This agreed with results from the other MA (Korsmo-Haugen et al, 2018) (6 RCTs, n=345) but disagreed with results of a sensitivity analysis excluding RCTs causing substantial heterogeneity (van Zuuren et al, 2018).

5.198 The evidence was graded as **inconsistent** because of disagreement between the results of the 2 MAs with those of a sensitivity analysis excluding RCTs causing substantial heterogeneity.

Longer-term data (≥12 months)

5.199 In total, 13 longer-term (≥12 months) primary RCTs were included in the MAs.

5.200 van Zuuren et al (2018) also conducted a MA at 24 months but results were not considered here because only 2 RCTs were included (see Table 4.1, chapter 4).

5.201 Korsmo-Haugen et al (2018): no difference in effect between lower and higher carbohydrate diets on serum HDL cholesterol (WMD 0.06 mmol/L, 95% CI -0.01 to 0.13, p=NR, I^2=71%, random-effects model; 10 RCTs, 1093 participants).

5.202 Huntriss et al (2018): significantly greater increase in serum HDL cholesterol with lower compared to higher carbohydrate diets (WMD 0.06 mmol/L, 95% CI 0.04 to 0.09, p<0.00001, I^2=1%, random-effects model; 7 RCTs, 645 participants).

5.203 van Zuuren et al (2018): significantly greater increase in serum HDL cholesterol with lower compared to higher carbohydrate diets (WMD 0.11 mmol/L, 95% CI 0.05 to 0.18, p=0.0007, I^2=66%, random-effects model; 4 RCTs, 375 participants). Results of analysis using a fixed-effects model agreed with those of the random-effects model (WMD 0.13 mmol/L, 95% CI 0.10 to 0.17, p<0.00001, I^2=66%, fixed-effects model; 4 RCTs, 375 participants). A sensitivity analysis excluding 1 RCT at high risk of bias also reported a significantly greater increase in serum HDL cholesterol in lower compared to higher carbohydrate diets (WMD 0.08 mmol/L, 95% CI 0.03 to 0.13, p=0.001, I^2=0%, random-effects model; 3 RCTs, 259 participants).

Summary: serum HDL cholesterol, longer term (≥12 months)

5.204 The largest MA (Korsmo-Haugen et al, 2018) (10 RCTs, n=1093) reported no difference in effect between lower and higher carbohydrate diets on serum HDL cholesterol in the longer term (≥12 months). This was in contrast with results of the 2 other MAs (Huntriss et al, 2018; 7 RCTs, n=645) (van Zuuren et al, 2018; 4 RCTs, n=375) and a sensitivity analysis excluding studies at high risk of bias (van Zuuren et al, 2018; 3 RCTs, n=259) that reported a significantly greater increase in serum HDL cholesterol with lower compared to higher carbohydrate diets.

5.205 The evidence was graded as **inconsistent** because of disagreement between results of the largest MA with those of the 2 other MAs.

Lower vs higher carbohydrate diets and serum HDL cholesterol
Shorter term (≥3 to 6 months) • **Inconsistent** evidence Longer term (≥12 months) • **Inconsistent** evidence

Medication use

5.206 One SR (Huntriss et al, 2018) assessed change in diabetes medication use as an outcome but provided only a descriptive analysis. The evidence was not reported separately by study duration.

5.207 Observations on medication use from the 3 other SRs with MAs are summarised in Annex 14 (Table A14.2).

5.208 Huntriss et al (2018) reported that 16 out of the 18 RCTs (n=2204) in the SR included participants on diabetes medication at trial start; 2 out of these 16 RCTs did not report on medication changes. All of the remaining 14 studies reported a reduced requirement for diabetes medication in the lower compared to the higher carbohydrate group. Eleven of these reported on significance of the difference in medication use between the lower and higher carbohydrate groups.

5.209 Out of the 11 studies that considered significance, 9 reported a significant reduction in diabetes medication use with lower compared to the higher carbohydrate diets: 2 in insulin, 2 in oral hypoglycaemic agents (Guldbrand et al, 2012; Shirai et al, 2013) and 5 in a combined diabetes medication score.

5.210 There was considerable variation in the reporting and measurement of medication use and change. It was not possible to assess consistency in effect size for this outcome since changes in medication use were generally not quantified.

Summary: medication use

5.211 One SR (Huntriss et al, 2018) assessed medication change as an outcome in a descriptive analysis. A significantly greater reduction in diabetes medication use was reported with lower compared to higher carbohydrate diets in 9 out of 11 studies which assessed significance. It was not possible to assess consistency in effect size.

5.212 This outcome was graded as **moderate** because of uncertainties and inconsistencies in the reporting and measurement of medication use and change.

Lower vs higher carbohydrate diets and medication use
Shorter-term (≥3 to 6 months) and longer-term (≥12 months) data were not reported separately. • Greater reduction in medication use in the lower carbohydrate group • **Moderate** evidence

Summary of evidence grading for all outcomes

5.213 Results of the evidence grading (strength of the evidence) together with the difference in effect (↓ greater decrease in lower carbohydrate group; ↑ greater increase in lower carbohydrate group; — no difference in effect between groups) are summarised in Table 5.4.

Table 5.4: Summary of strength of the evidence on effects of lower vs higher carbohydrate diets on markers and clinical outcomes of T2D

Outcome	Shorter-term data (≥3 to 6 months)		Longer-term data (≥12 months)	
	Difference in effect	**Strength of evidence**	**Difference in effect**	**Strength of evidence**
Body weight	Inconsistent		—	Adequate
HbA1c	↓	Adequate	Inconsistent (≥12 to <24 months)	
			—	Adequate (24 months)
Fasting plasma glucose	↓	Moderate	Insufficient	
Serum total cholesterol	—	Moderate	—	Adequate
Serum triacylglycerol	↓	Adequate	Inconsistent	
Serum LDL cholesterol	—	Adequate	—	Adequate
Serum HDL cholesterol	Inconsistent		Inconsistent	
Medication use	↓ Moderate (shorter- and longer-term data not reported separately)			

Adverse events

SRs with MAs

5.214 None of the 4 SRs with MAs systematically assessed adverse events.

5.215 Korsmo-Haugen et al (2018) reported that 13 out of the 23 RCTs included in their SR described adverse events. Out of these: 1 RCT, of participants with renal failure, reported a worse outcome relating to indicators of nephropathy with the higher carbohydrate diet (Facchini & Saylor, 2003); the other RCTs reported no serious adverse events and no difference between groups in reported mild adverse events such as mild hypoglycaemia.

5.216 Sainsbury et al (2018) reported that they had not assessed the safety of lower carbohydrate diets, including the potential for micronutrient deficiencies and increased frequency of hypoglycaemic episodes, but noted that 2 RCTs (Yamada et al, 2014; Sato et al, 2017) had reported 3 and 4 hypoglycaemic episodes respectively among participants in the lower carbohydrate groups.

5.217 Huntriss et al (2018) and van Zuuren et al (2018) did not report on adverse events.

Primary RCTs

5.218 Thirteen of the primary RCTs included in the 4 SRs with MAs reported on occurrence of adverse events during the study (see Annex 18, Table A18.1). None reported any serious adverse events related to the diet. The most common adverse events that were experienced included gastroenteritis, nausea, vomiting and headaches.

5.219 There were no significant differences in reported adverse events between lower and higher carbohydrate groups except in 1 RCT (Goday et al, 2016) that prescribed ‘very low’ carbohydrate intakes (<50g/day): mild adverse events (such as headache and nausea,) were reported by 80% of participants in the ‘very low’ carbohydrate group compared to 41% in the higher carbohydrate group ($p<0.001$).

Potential long-term concerns

5.220 The implications of long-term restriction of carbohydrates in adults with T2D are currently unknown since there is a lack of data from longer-term (≥12 months) intervention studies.

5.221 The reduced carbohydrate intake in lower carbohydrate diets is usually replaced by increased consumption of protein or fat. Although there was some overlap in SFA intakes between the lower and higher carbohydrate groups in the primary studies, they were generally higher in the lower carbohydrate diets (6 to 20% TE

from SFA) compared with higher carbohydrate diets (8 to 13% TE from SFA). This is a potential concern since long-term higher consumption of SFAs increases risk of CVD and coronary heart disease (CHD) events (SACN, 2019). However, in the evidence considered, increased concentrations of surrogate markers of CVD risk (serum total cholesterol, triacylglycerol and LDL cholesterol) were not observed over the study duration periods.

Summary

5.222 Evidence from the primary RCTs included in the SRs with MAs suggests little difference in adverse events between lower and higher carbohydrate diets in the short term (≥3 to 6 months).

5.223 The implications of longer-term (≥12 months) consumption of lower carbohydrate diets in adults with T2D are unknown.

6 Overall summary and conclusions

Summary

6.1 The purpose of this report was to review the evidence on 'low' carbohydrate diets compared to current UK government advice on carbohydrate intake for adults with T2D (that about 50% TE should be obtained from carbohydrates). However, since there is no agreed definition of a 'low' carbohydrate diet, comparisons in this report were between lower and higher carbohydrate diets.

Terms of reference

6.2 The terms of reference were to:

- review the evidence on lower carbohydrate diets (alongside higher fat and/or higher protein) compared to current government advice for adults with T2D
- consider the impact, in adults with T2D, of lower compared with higher carbohydrate diets on markers and clinical outcomes of T2D including any potential adverse effects
- make recommendations based on the review of the evidence.

Definition of diets containing different amounts of carbohydrates

6.3 For the purpose of this review, to allow comparisons of carbohydrate intakes across studies, the following categories were adopted to group carbohydrate intakes (g/day or % TE) as 'very low', 'low', 'moderate' and 'high' (see Table 6.1).

Table 6.1: Categories of dietary carbohydrate intakes[1]

Carbohydrate category	Amount of carbohydrate	
	g/day	**% TE** (based on 2000 kcal/day)
Very low[2]	20 to 50	≤10
Low	>50 to <130	>10 to <26
Moderate	130 to 230	26 to 45
High	>230	>45

[1] Based on Feinman et al (2015) and Accurso et al (2008)

[2] Also referred to as ketogenic diets

6.4 According to these categories, current government recommendations on carbohydrate intake for the general population (50% TE) are classified as ‘high’.

Assessment of the evidence

6.5 The report is based on evidence provided by SRs with MAs of RCTs (minimum duration of 3 months) comparing the impact of lower vs higher carbohydrate diets on markers and clinical outcomes of T2D.

6.6 Evidence from clinical practice studies was not considered because these studies did not meet the inclusion criteria for study selection.

6.7 Primary outcomes of interest were body weight (≥12 months) and HbA1c (≥3 months). Secondary outcomes were: body weight (≥3 to <12 months), fasting plasma glucose (≥3 months), blood lipids (serum total cholesterol; serum triacylglycerol; serum LDL cholesterol; serum HDL cholesterol; serum total cholesterol:HDL cholesterol ratio) (≥3 months); and medication use. None of the SRs with MAs considered serum total cholesterol:HDL cholesterol ratio as an outcome.

6.8 In the evidence considered, outcomes were assessed in the shorter term (≥3 to 6 months) and longer term (≥12 months).

6.9 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 used to grade the evidence and draw conclusions.

6.10 The evidence was graded as **adequate**, **moderate**, **limited**, **inconsistent** or **insufficient**. Only outcomes where the evidence base was graded as adequate or moderate were used to inform the recommendations.

Characteristics of primary RCTs included in MAs

6.11 In total, 31 RCTs (36 publications) were included in the MAs of the 4 SRs with MAs. Out of the 36 publications:

- 18 reported outcomes only in the shorter term: all except 2 reported outcomes between 3 to 6 months (1 reported at 8 months and 1 at 9 months)
- 18 reported outcomes in the longer term (≥12 months); 10 of these also assessed outcomes in the shorter term (at 3 and/or 6 months) and 6 assessed outcomes beyond 12 months (4 at 24 months; 2 at 48 months).

Populations

6.12 Sample sizes of studies ranged from 24 to 419 participants (mean, n=100). Thirty out of 31 RCTs included both men and women; 1 included only women.

6.13 Out of 10 RCTs that reported ethnicity, the average proportion of White participants was 54.5%. Ethnicity was not reported in 21 RCTs but most were set in countries with predominantly White populations.

6.14 The average BMI (reported in 26 RCTs) was 33 kg/m^2 in the lower carbohydrate groups and 34 kg/m^2 in the higher carbohydrate groups.

Macronutrient and energy intakes

6.15 Prescribed carbohydrate intakes ranged between 14 to 50% TE (median 40% TE) in the lower carbohydrate groups and 23 to 65% TE (median 55% TE) in the higher carbohydrate groups.

6.16 Reported macronutrient and energy intakes are summarised in Table 6.2 below (details of current UK government recommendations for macronutrient and energy intakes are provided in Annex 1).

Table 6.2: Reported macronutrient and energy intakes in the primary RCTs in the shorter (≥3 to 6 months) and longer term (≥12 months)

Macronutrient/Energy		**Reported mean intakes** median (range)	
		Lower carbohydrate	**Higher carbohydrate**
Carbohydrate (%TE)			
Shorter term [category]		37 (13 to 47) [low to high]	50 (41 to 55) [moderate to high]
Longer term [category]		39 (17 to 46) [low to high]	48 (43 to 54) [moderate to high]
Fats (%TE)			
Shorter term	Total	40 (18 to 59)	29 (23 to 36)
	SFA	10 (6 to 20)	8 (8 to 12)
	PUFA	6 (4 to 12)	5 (4 to 7)
	MUFA	17 (8 to 30)	11 (10 to 12)
Longer term	Total	44 (31 to 58)	31 (26 to 40)
	SFA	12 (10 to 19)	10 (8 to 13)
	PUFA	8 (6 to 13)	6 (4 to 7)
	MUFA	16 (13 to 29)	11 (11 to 13)
Protein (%TE)			
Shorter term		26 (19 to 37)	19 (16 to 23)
Longer term		23 (16 to 27)	19 (16 to 21)
Energy (kcal/day; kJ/day)			
Shorter term		1557 (1273 to 2029) 6512 (5326 to 8489)	1549 (1197 to 1785) 6479 (5008 to 7468)
Longer term		1708 (1251 to 2222) 7144 (5234 to 9297)	1747 (1420 to 2222) 7309 (5941 to 9297)

Limitations in the evidence base

6.17 Several limitations were identified in the quality of the evidence base.

6.18 One of the most important limitations was the lack of an agreed definition for a 'low' carbohydrate diet. In the 4 SRs with MAs that were considered in evaluating and grading the evidence, the cut-offs for defining a low carbohydrate diet were: ≤40% TE (2 SRs), ≤45% TE (1 SR), no specific cut-off (1 SR).

6.19 In the primary RCTs included in the MAs of the 4 SRs, there was considerable overlap between prescribed carbohydrate intakes in the lower (14 to 50% TE) and higher (23 to 65% TE) carbohydrate groups. There was also overlap in reported mean carbohydrate intakes between lower and higher carbohydrate groups:

- shorter-term (≥3 to 6 months): 13 to 47% TE in the lower carbohydrate groups; 41 to 55% TE in the higher carbohydrate groups
- longer term (≥12 months): 17 to 46% TE in the lower carbohydrate groups; 43 to 54% TE in the higher carbohydrate groups.

6.20 Out of the 30 publications that reported mean intakes of carbohydrates, most comparisons (16 publications), according to categories of carbohydrate intakes, were between 'moderate' vs 'high' carbohydrate intakes; only 4 publications compared 'low' vs 'high' carbohydrate intakes.

6.21 As well as being very heterogeneous in the amounts of carbohydrates prescribed and reported in the lower carbohydrate categories, the primary RCTs varied in the type and amount of macronutrient that replaced carbohydrate and in the duration and intensity of advice given to participants on following their prescribed diets. Very few trials included details on the type of carbohydrate consumed (for example, wholegrain, refined grain, free sugars, fibre) or considered how this could affect the outcomes under consideration. There was also limited information on adherence to the prescribed intakes throughout the full duration of study or consideration of how adherence might impact outcomes.

6.22 An important limitation was the inconsistent assessment and reporting of medication use. In some studies, dosage of diabetes medication was adjusted proactively before the study while in others it was adjusted during the study to minimise risk of hypoglycaemia. Medication use was also a potential confounder for change in HbA1c, one of the primary outcomes, since reducing medication in the lower carbohydrate group could reduce differences in HbA1c change between the intervention groups.

6.23 Another limitation was that most shorter-term studies did not assess outcomes beyond 6 months and few longer-term studies assessed outcomes beyond 12 months.

6.24 Risk of bias was assessed as high or unclear in most of the primary RCTs included in the 4 SRs with MAs. This reduces the confidence that can be placed on the estimates of the effects.

6.25 The majority of participants in the primary RCTs were living with overweight (BMI ≥25 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2). It is not known if reported effects can be generalised to adults with a healthy weight (BMI ≥18.5 to <25 kg/m^2).

6.26 Most of the primary RCTs did not report ethnicity of participants and none performed subgroup analyses based on ethnicity. It is not known, therefore, if the reported effects of lower carbohydrate diets differ in individuals of different ethnicities.

Evidence grading

Body weight

6.27 The evidence was **inconsistent** in the shorter term (≥3 to 6 months) because there was a greater reduction in body weight with lower compared to higher carbohydrate diets at 3 months, but this difference was not observed between 3 and 6 months or at 6 months.

6.28 There was **adequate** evidence for no difference in effect between lower and higher carbohydrate diets in reducing body weight in the longer term (≥12 months).

HbA1c

6.29 There was **adequate** evidence of a greater reduction in HbA1c with lower compared to higher carbohydrate diets in the shorter term (≥3 to 6 months).

6.30 The evidence was **inconsistent** in longer-term studies with a duration of 12 up to 24 months.

6.31 There was **adequate** evidence for no difference between lower and higher carbohydrate diets on HbA1c change in longer-term studies at 24 months.

Fasting plasma glucose

6.32 There was **moderate** evidence of a greater reduction in fasting plasma glucose with lower compared to the higher carbohydrate diets in the shorter term (≥3 to 6 months).

6.33 There was **insufficient** evidence to assess if there was a difference between lower and higher carbohydrate diets on fasting plasma glucose in the longer term (≥12 months).

Serum total cholesterol

6.34 There was **moderate** evidence for no difference in effect between lower and higher carbohydrate diets in reducing serum total cholesterol in the shorter term (≥3 to 6 months).

6.35 There was **adequate** evidence for no difference in effect between lower and higher carbohydrate diets in reducing serum total cholesterol in the longer term (≥12 months).

Serum triacylglycerol

6.36 There was **adequate** evidence of a greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets in the shorter term (≥3 to 6 months).

6.37 The evidence was **inconsistent** in the longer-term (≥12 months).

Serum LDL cholesterol

6.38 There was **adequate** evidence for no difference in effect between lower and higher carbohydrate diets on change in serum LDL cholesterol in the shorter term (≥3 to 6 months) and in the longer term (≥12 months).

Serum HDL cholesterol

6.39 The evidence on lower compared to higher carbohydrate diets on serum HDL cholesterol was **inconsistent** in the shorter term (≥3 to 6 months) and longer term (≥12 months).

Medication use

6.40 There was **moderate** evidence of a greater reduction in medication use with lower compared to higher carbohydrate diets. This outcome was not assessed according to study duration. It was not possible to assess consistency in effect size.

Summary of evidence grading for all outcomes

6.41 Results of the evidence grading are summarised in Table 6.3.

Table 6.3: Summary of strength of the evidence on effects of lower vs higher carbohydrate diets on markers and clinical outcomes of T2D

Outcome	Shorter term (≥3 to 6 months)		Longer term (≥12 months)	
	Difference in effect	**Strength of evidence**	**Difference in effect**	**Strength of evidence**
Body weight	Inconsistent		—	Adequate
HbA1c	↓	Adequate	Inconsistent (≥12 to <24 months)	
			—	Adequate (24 months)
Fasting plasma glucose	↓	Moderate	Insufficient	
Serum total cholesterol	—	Moderate	—	Adequate
Serum triacylglycerol	↓	Adequate	Inconsistent	
Serum LDL cholesterol	—	Adequate	—	Adequate
Serum HDL cholesterol	Inconsistent		Inconsistent	
Medication use	↓ Moderate (shorter- and longer-term data not reported separately)			

Difference in effect: ↓ greater reduction in lower carbohydrate group; ↑ greater increase in lower carbohydrate group; — no difference between groups.

Adverse events

6.43 In the shorter term (≥3 to 6 months), there was no evidence of any difference in adverse events between lower and higher carbohydrate intakes in adults with T2D.

6.44 The health effects of longer-term (≥12 months) consumption of lower carbohydrate diets in adults with T2D are unknown.

Conclusions

6.45 From the evidence considered, it was not possible to assess the impact of a ‘low’ compared to a ‘high’ carbohydrate diet on markers and clinical outcomes of T2D in adults with T2D. This was because:

- the definition of a low carbohydrate diet varied widely across the primary RCTs, with prescribed carbohydrate intakes in lower carbohydrate groups ranging from 14 to 50% TE (median, 40% TE)
- there was overlap in reported mean carbohydrate intakes between the lower and higher carbohydrate diets in the shorter term (≥3 to 6 months) (13 to 47% TE in the lower and 41 to 55% in the higher carbohydrate diets) and in the longer term (≥12 months) (17 to 46% TE in the lower and 43 to 54% in the higher carbohydrate diets)
- according to categories of carbohydrate intake, reported mean carbohydrate intakes in the lower carbohydrate groups were moderate (26 to 45% TE) in the majority of primary RCTs.

6.46 Comparisons, therefore, were largely between lower and higher rather than ‘low’ and ‘high’ carbohydrate diets. This limits interpretation of the evidence for any benefits or harms of a ‘low’ compared to a ‘high’ carbohydrate diet.

6.47 Overall, the evidence suggests beneficial effects of lower carbohydrate diets for some outcomes (HbA1c, fasting plasma glucose, serum triacylglycerol) in the shorter term (up to 6 months). Since the shorter-term assessments did not report outcomes between 6 and 12 months it is uncertain if the suggested benefits are maintained beyond 6 months.

6.48 Although there was no consistent evidence of reductions in body weight with lower carbohydrate diets it is not possible, from the evidence considered, to separate the effects of weight change from effects of change in carbohydrate intake.

6.49 Lower carbohydrate diets may allow reductions in diabetes medication, but interpretation is complicated by inconsistencies in reporting and measurement of changes in medication use.

6.50 No differences were observed between higher and lower carbohydrate diets on serum total or LDL cholesterol either in the shorter (≥3 to 6 months) or longer term (≥12 months). Evidence on HDL cholesterol was inconsistent in the shorter (≥3 to 6 months) and longer term (≥12 months).

6.51 In general, there was no difference in adverse events between lower and higher carbohydrate diets but study duration did not extend beyond 12 months in the majority of primary RCTs.

6.52 The overall quality of the evidence base was limited by a number of uncertainties in the data, including: variability in the definition of a low carbohydrate diet; smaller than prescribed differences in reported carbohydrate intakes between lower and higher carbohydrate diets; inherent inaccuracies in estimates of self-reported dietary intakes; and lack of information on adherence to prescribed diets.

6.53 An important limitation was that risk of bias was high or unclear in most of the primary RCTs that were included in the MAs. This reduces the confidence that can be placed on the estimates of the effects of lower carbohydrate diets on the markers of T2D and clinical outcomes under consideration.

6.54 Another important limitation in the evidence base was that shorter-term studies did not assess outcomes beyond 6 months and few longer-term studies assessed outcomes beyond 12 months.

6.55 The majority of participants in the primary RCTs were living with overweight (BMI ≥25 to <30 kg/m^2) or obesity (BMI ≥30 kg/m^2). It is not known if reported effects can be generalised to adults living with T2D with a healthy weight (BMI ≥18.5 to <25 kg/m^2).

6.56 It is not known if the reported effects of lower carbohydrate diets apply to individuals of different ethnicities since the majority of primary RCTs did not report ethnicity of participants and most were conducted in populations that were predominantly White. In those that reported ethnicity, none conducted subgroup analyses based on ethnicity.

6.57 This report did not assess evidence on the effect of lower carbohydrate diets in the general population without T2D. It is not known if the reported effects of lower carbohydrate diets in adults with T2D apply to the general adult population without T2D.

6.58 Several gaps were identified in the evidence base:

- effects of lower carbohydrate diets on individuals living with T2D from minority ethnic population groups was not considered
- no trials provided information about types of carbohydrate consumed (for example, wholegrain, refined grain, free sugars, fibre) or considered how this could affect the outcomes of interest
- the potential impact of increasing the proportions of other macronutrients (fats and/or proteins) to compensate for reduced carbohydrate intake in the lower carbohydrate groups, or the type of macronutrient (for example, saturated or unsaturated fats; plant or animal-based proteins), on markers and clinical outcomes of T2D was generally not considered
- few trials assessed adherence to dietary interventions throughout the study duration or considered how adherence might impact the outcomes

- few trials assessed longer-term effects (beyond 12 months) of lower carbohydrate diets
- no trials considered clinical endpoints such as diabetes complications, CVD events or mortality.

7 Recommendations

7.1 The recommendations are applicable to adults living with T2D and overweight or obesity. There was insufficient evidence to make recommendations for adults living with T2D without overweight or obesity. This report did not assess evidence on the effect of lower carbohydrate diets in the general population without T2D.

7.2 For adults living with T2D and overweight or obesity, a lower carbohydrate diet can be recommended by clinicians as an effective short-term option (up to 6 months) for improving glycaemic control and serum triacylglycerol concentrations.

7.3 Individuals living with T2D and overweight or obesity, who choose a lower carbohydrate diet, should include wholegrain or higher fibre foods, a variety of fruits and vegetables and limit intakes of saturated fats, reflecting current dietary advice for the general population.

7.4 Since the majority of individuals living with T2D have overweight or obesity, weight management remains the primary goal for improving glycaemic control and reducing CVD risk. Health professionals should support any evidence-based dietary approach that helps individuals with T2D to achieve long-term weight reduction.

7.5 Adults living with T2D and overweight or obesity who change to a lower carbohydrate diet and are taking diabetes medication may be at risk of hypoglycaemia. It is recommended that they receive advice and support from their health care team to manage this risk and to make adjustments to their medication as required.

8 Research recommendations

8.1 A number of limitations and gaps in the evidence base were identified and these informed the research recommendations.

8.2 Important limitations highlighted in this report were inconsistencies in the definition of a low carbohydrate diet and in the reporting of medication use. In addition, few trials reported on adherence to prescribed diets. To enable more robust comparisons and conclusions to be drawn about the impact of lower carbohydrate diets, it is recommended that future research should:

- develop and agree consistent international definitions for very low, low, moderate and high carbohydrate diets
- report medication usage in terms of quantitative details and analysis
- measure and report adherence to prescribed dietary interventions
- ensure robust study design in line with best international standards.

8.3 Areas recommended for future research are summarised below.

8.4 Consideration of the effects and effectiveness of lower carbohydrate diets for adults living with T2D:

- from minority ethnic population groups
- with a healthy weight (BMI ≥18.5 to <25 kg/m^2).

8.5 Consideration of the potential impact on markers and clinical outcomes of T2D of:

- type of carbohydrate (for example, wholegrain, refined grain, free sugars, fibre) being consumed in the dietary groups
- increasing the proportions and types of other macronutrients (for example fats and/or proteins) to compensate for reduced carbohydrate intakes in lower carbohydrate diet groups
- lower carbohydrate diets independent of weight loss
- lower carbohydrate diets compared with lower energy diets
- adherence to prescribed diets.

8.6 Consideration of the health implications of lower carbohydrate diets over several years, for adults living with T2D, including both potential beneficial and adverse effects on markers of nutritional status (such as micronutrient status) and on clinical endpoints (such as diabetes complications, CVD events or mortality).

8.7 Consideration of behaviour change interventions to support people with T2D to achieve a lower carbohydrate diet that could be implemented in routine care settings.

8.8 Reanalysis of existing data from RCTs; for example, conducting individual participant data meta-analysis using consistent definitions (for example for ‘low’ carbohydrate diet) and focusing on some of the issues identified above (such as carbohydrate type) and subgroups of interest (such as minority ethnic population groups).

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Annexes

Annex 1: Current UK government dietary recommendations for the general population

Table A1.1: UK government dietary recommendations for energy and macronutrients for men and women in the UK

Energy	2500 kcal/day, men; 2000 kcal/day, women[5]
Proteins[1]	0.75g per kilogram of bodyweight[6]
Total fats[2]	Reduce to about 35% of dietary energy[7]
Saturated fats[2]	Reduce to no more than about 10% of dietary energy[8]
MUFA[2]	No specific recommendations[9]
n-6 PUFA[2]	No further increase in average intakes; proportion of population consuming in excess of about 10% of energy should not increase[10]
Linoleic acid[1]	At least 1% of total energy
Long chain n-3 PUFA[3]	Increase from 0.2 to 0.45 g/day[11]
Alpha linolenic acid[1]	At least 0.2% of total energy
Trans fats[2]	No more than about 2% of dietary energy
Carbohydrates[4]	Approximately 50% of total dietary energy
Free sugars[4]	Should not exceed 5% of total dietary energy
Dietary fibre[4]	30g/day[12]

[1] COMA Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (1991).

[2] COMA Nutritional Aspects of Cardiovascular Disease (1994).

[3] SACN advice on fish consumption: benefits and risks (2004). SACN endorsed the population recommendation (including pregnant women) to eat at least 2 portions of fish/week, of which 1 should be oily; this contains approximately 0.45 g/day long chain n-3 PUFA.

[4] SACN Carbohydrates and Health (2015) - recommendations for population aged 2 years and over.

[5] Figures based on UK government advice. They are not in line with SACN Dietary Reference Values for Energy (2011) (2605 kcal/day, men; 2079 kcal/day, women). These were not adopted by government because of issues relating to overweight and obesity in the UK.

[6] Reference Nutrient Intake (RNI) for adults aged 19 to 50 years (these vary depending on age, sex and whether pregnant or breastfeeding).

[7] COMA Nutritional Aspects of Cardiovascular Disease (1994).

[8] COMA Nutritional Aspects of Cardiovascular Disease (1994) recommends that the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than

about 10%. This was based on total dietary energy (which includes any intake from alcohol). The COMA DRV report (1991) noted that the corresponding recommendation for food energy (which excludes any intake from alcohol) would be 11%. The 1994 report stated that 'the precision of our recommendations does not warrant such a distinction. These do not therefore take account of the small, variable differences between fat as a proportion of total or of food (ie excluding alcohol) energy.

[9] COMA Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (1991) recommended that cis-MUFA (principally oleic acid) should continue to provide on average 12% of dietary energy for the population.

[10] COMA Nutritional Aspects of Cardiovascular Disease (1994) recommended 'an increase in the population average consumption of long chain n-3 PUFA from about 0.1 g/day to about 0.2 g/day (1.5 g/week)'.

[11] COMA Nutritional Aspects of Cardiovascular Disease (1994) recommends no further increase in average intakes of n-6 PUFA and recommends that the proportion of the population consuming excess of about 10% energy should not increase.

[12] DRV for adults aged 19 years and over.

Annex 2: Search strategy

Table A2.1: Details of literature search

Search strategy for Ovid Medline			**Results**	
Population terms	**Intervention terms**	**Database**	**Number of hits**	**Exclusive**
type 2 adj2 diabet*	low* carb* adj3 diet*	Ovid Medline (1946-2017 Oct)	1753	1597
(note this will pick up: type 2 diabetes, type 2 diabetic, diabetes mellitus type 2)	carbohydrate* adj2 restrict*	Ovid Embase (1980-2017 week 41)	2498	1239
type II adj2 diabet*	high* carb* adj3 diet*	Cochrane Library (CDSR and DARE) - Issue 10 of 12, October 2017	91	80
(note this will pick up: type II diabetes, type II diabetic, diabetes mellitus type II)	carbohydrate* adj2 reduc*	NICE Evidence	100	85
T2D	ketogenic diet*	TRIP	189	158
Diabetes Mellitus, Type 2/	glycemic index	Google Scholar	29*	10
	glycaemic index		**TOTAL =**	**3169**
	atkins adj3 diet*			
	south beach adj3 diet*		* only relevant included	
	zone adj3 diet*			
	dukan adj3 diet*			
	dietary carb*			

Search strategy for Ovid Medline			**Results**	
Population terms	**Intervention terms**	**Database**	**Number of hits**	**Exclusive**
Note: for Cochrane Library, change adj to NEXT	Diet, Carbohydrate-Restricted/			
	Glycemic Index/			
TRIP, NICE Evidence: carbohydrate diet type 2 diabetes	Ketogenic Diet/			
Google Scholar: allintitle: carbohydrate diet type 2 diabetes	Diet, Paleolithic/			

Annex 3: Selection of studies

Table A3.1: Studies excluded based on assessment of full-text articles (1st and 2nd screenings)

Studies		Reasons for exclusion
1st screening		
1	Clifton P, Carter S, Headland M & Keogh J (2015) Low carbohydrate and ketogenic diets in type 2 diabetes. Curr Opin Lipidol 26(6):594-595.	Non-SR/MA/PA
2	D'Arrigo T (2007) Low-fat vs. low-carb. What really works? Diabetes Forecast. 60(7):16.	Non-SR/MA/PA
3	Bravata DM, Sanders L, Huang J, Krumholz HM, Olkin I, Gardner CD & Bravata MD (2003) Efficacy and safety of low-carbohydrate diets: a systematic review. JAMA 289(14):1837.	Included participants with/without T2D. Insufficient information and/or separate analyses of T2D participants.
4	Dyson PA (2008) A review of low and reduced carbohydrate diets and weight loss in type 2 diabetes. J Human Nutr Diet. 21(6):530-538.	Non-SR/MA/PA
5	Haugen H-K (2014) The effectiveness of a low-carbohydrate diet in management of type 2 diabetes-A systematic review of the current literature. Høgskolen i Oslo og Akershus.	Master's thesis
6	Julienne KK, Darby EG, Timothy EC, Edward WL, Mary A & Karen LM (2007) Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 108:91	Same study already included (Kirk et al 2008)
7	Santos F, Esteves S, da Costa Pereira A, Yancy Jr W & Nunes J (2012) Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev. 13(11):1048-1066.	Participants without T2D

Studies		Reasons for exclusion
8	Moore H, Summerbell C, Hooper L, Cruickshank K, Vyas A, Johnstone P et al (2004). Dietary advice for treatment of type 2 diabetes mellitus in adults. Cochrane. (2):004097.	Same study (updated) already included (Nield et al 2007)
2nd screening		
9	Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M & Margolis KL (2008) Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 108(1):91-100.	Includes studies with duration less than 3 months (11 out of 13 studies)
10	Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Sato M et al (2009) Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care. 32(5):959-965.	Includes studies with duration less than 3 months (20 out of 22 studies)
11	Garg A (1998) High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr 67(3 Suppl):577S-582S.	All included studies were less than 3 months duration
12	Nield L, Moore HJ, Hooper L, Cruickshank JK, Vyas A, Whittaker V et al (2007) Dietary advice for treatment of type 2 diabetes mellitus in adults. Cochrane Database of Systematic Reviews (3):CD004097.	Wide range of dietary advice assessed, focus not on carbohydrates
13	Anderson JW, Randles KM, Kendall CW & Jenkins DJ (2004) Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. J Am Coll Nutr. 23(1):5-17.	Includes studies with duration less than 3 months (20 out of 24 studies)
14	Ajala O, English P & Pinkney J (2013) Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes (structured abstract). Am J Clin Nutr [Online]. 97.	Did not offer any additional information to that covered by the more recent reviews
15	Castaneda-Gonzalez LM, Bacardi Gascon M & Jimenez Cruz A (2011) Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. Nutricion Hospitalaria. 26:1270-1276.	Did not offer any additional information to that covered by the more recent reviews

Table A3.2: List of studies highlighted by interested parties through the call for evidence and reasons for exclusion

	Studies	Reasons for exclusion
1	Sartorius K, Sartorius B, Madiba TE & Stefan C (2018) Does high-carbohydrate intake lead to increased risk of obesity? A systematic review and meta-analysis. BMJ Open. 8(2):e018449.	Participants without T2D
2	Kwon YJ, Lee HS & Lee JW (2017) Association of carbohydrate and fat intake with metabolic syndrome. Clin Nutr. S0261-5614(17):30233-30239.	Not RCT
3	Te Morenga L, Docherty P, Williams S & Mann J (2017) The Effect of a Diet Moderately High in Protein and Fiber on Insulin Sensitivity Measured Using the Dynamic Insulin Sensitivity and Secretion Test (DISST). Nutrients. 9(12).	Study duration less than 3 months
4	Zinn C, McPhee J, Harris N, Williden M, Prendergast K & Schofield G (2017) A 12-week low-carbohydrate, high-fat diet improves metabolic health outcomes over a control diet in a randomised controlled trial with overweight defence force personnel. Appl Physiol Nutr Metab 42(11):1158-1164.	Participants without T2D
5	Juraschek SP, Miller ER 3rd, Selvin E, Carey VJ, Appel LJ, Christenson RH et al (2016) Effect of type and amount of dietary carbohydrate on biomarkers of glucose homeostasis and C reactive protein in overweight or obese adults: results from the OmniCarb trial. BMJ Open Diabetes Res Care. 4(1):e000276. eCollection 2016.	Participants without T2D
6	Ruiz-González I, Fernández-Alcántara M, Guardia-Archilla T et al (2016) Long-term effects of an intensive-practical diabetes education program on HbA1c and self-care. Appl Nurs Res. 13-18.	Participants with T1D
7	Nuttall FQ, Almokayyad RM & Gannon MC (2015) Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes. Metabolism. 64(2):253-262.	Study duration less than 3 months

	Studies	Reasons for exclusion
8	Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA et al (2015) Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 102(4):780-790.	Excluded: already included in Schwingshackl et al 2018 and Huntriss et al 2018
9	Martens EA, Gatta-Cherifi B, Gonnissen HK & Westerterp-Plantenga MS (2014) The potential of a high protein-low carbohydrate diet to preserve intrahepatic triglyceride content in healthy humans. PLoS One. 9(10):e109617.	Participants without T2D
10	Sacks FM, Carey VJ, Anderson CA, Miller ER 3rd, Copeland T, Charleston J et al (2014) Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. JAMA. 312(23):2531-2541.	Participants without T2D
11	Luley C, Blaik A, Reschke K, Klose S & Westphal S (2011) Weight loss in obese patients with type 2 diabetes: effects of telemonitoring plus a diet combination - the Active Body Control (ABC) Program. Diabetes Res Clin Pract. 91(3):286-292.	Published before most recent SR, MA or PA
12	Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD et al (2018) Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes Obes Metab.	RCT included in eligible SR with MA
13	Saslow LR, Daubenmier JJ, Moskowitz JT, Kim S, Murphy EJ, Phinney SD et al (2017) Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes. 7(12):304.	RCT included in eligible SR with MA

Annex 4: Summaries of systematic reviews with meta-analyses and network meta-analysis published after September 2018

Table A4.1: Systematic reviews with meta-analyses

First author (year)	Methods	Included studies	Results of meta-analyses (WMD in change) (95% CI))	Limitations and study conclusions (as assessed by authors)
Goldenberg et al (2021) **Aim**: To determine the efficacy and safety of low carbohydrate diets and very low carbohydrate diets for people with T2D. **Countries**: Not reported. **Funding source**: funded in part by Texas A&M University **Declarations of interest:** BCJ receives funds from Texas A&M AgriLife Research for research related to saturated and polyunsaturated	**Search period**: Inception to 25 August 2020 **Databases searched**: CENTRAL, Medline, Embase, CINAHL, and CAB abstracts. Also searched 3 trial registries (for example, clinicaltrials.gov) and 4 additional grey literature sources. **Language restrictions**: None. **Inclusion criteria:** • RCTs comparing LCDs (<26% TE or <130 g/day from CHOs) with any control diet higher in CHOs (≥26%) (with or without exercise or lifestyle and behavioural recommendations) for ≥12 weeks in adults with T2D **Exclusion criteria:** None reported. **Outcome measures**: • Primary: T2D remission (defined as HbA1c <6.5% or FBG <7.0 mmol/L), with or without use of diabetes	**Number of studies**: 23 (n=1357) **Study duration**: 3 m to 2 y **Study population**: • Age range (mean): 47 to 67 y • BMI: >23 to 65 • Sex: male (6), both (17) • Ethnicity: NR • Medication: only reported whether trials included participants using insulin; did not include, 7 trials; did include, 14 trials; not reported, 2 trials • Physical activity: not reported **Intervention**: **LCD**: (CHO <26% TE) • Ranged from 20 to 26% TE/<20 to <130 g per day	**Reported CHO intake**: NR **Missing outcome data**: Reported in 18 studies; out of these, 10 reported > 20% data missing. **Outcomes** (reported at 6 and 12m): <u>HbA1c (%)</u> • 6 m (17 studies; n=747): –0.47 (–0.60 to –0.34), p=NR, I^2=NR • 12 m (8 studies; n=489): –0.23 (–0.46% to 0.00), p=NR, I^2=NR <u>Weight (kg)</u> • 6 m (18 studies, n=882): –3.46 (–5.25 to –1.67), p<0.001, I^2=63% • 6 m, subgroup analysis of studies at low risk of bias (6 studies, n=171): –7.41 (–9.75, –5.08), p<0.001, I^2=0% • 12 m (7 studies, 499 participants): 0.29 (–1.02 to 1.60), p=NR, I^2=NR <u>Fasting plasma glucose (mmol/L)</u> • 6 m (14 studies, n=611): –0.73 (–1.19, –0.27), p=NR, I^2=NR • 12 m (6 studies, n=365): 0.06 (–0.37, 0.48), p=NR, I^2=NR	**Limitations**: 18/23 (78%) studies used LFDs as a comparator, limiting applicability of results to other dietary regimens. Caloric restriction was a potential confounding factor. Unclear whether any purported benefit was due to CHO or caloric restriction. Trials informing 6m endpoint varied between 3 and 8 m (7/14 (50%) reported data at 3 to <6 m and 7/14 (50%) reported at 6 to 9 m). Review focused on studies defined by macronutrient quantity. Unable to consider effects of dietary quality due to lack of reporting in eligible trials.

First author (year)	Methods	Included studies	Results of meta-analyses (WMD in change) (95% CI))	Limitations and study conclusions (as assessed by authors)
fats; GB is author of the CSIRO Low Carb Diet Book but does not receive any financial royalties or funds from this publication.	medication; weight loss, HbA1c, FBG, adverse events • Secondary: QoL, medication reduction, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, HOMA-IR, C reactive protein. **Statistical analysis**: • Random-effects model • Heterogeneity assessed using I^2 statistic and X^2 test for homogeneity (50% to 90%, substantial heterogeneity; 75% to 100%, considerable heterogeneity) • Subgroup analyses for primary outcomes: amount of CHO restriction, behavioural support intensity, comparator diet, isocaloric comparator, caloric restriction, inclusion of patients who used insulin, and adherence **Study quality**: GRADE and Cochrane risk of bias tool. **Publication bias**: funnel plots when ≥10 trials included; Egger's regression test for continuous outcomes and Harbord score for dichotomous outcomes.	**Comparator**: Any higher CHO diet (≥26% TE) (CHO intake not reported) • Low fat (18) • Low GI (3) • No treatment (1) • 'Standard' (1) **Authors' evaluation**: Risk of bias Overall, 59.4% of outcomes rated as having some concern or high risk of bias; 40.6% of outcomes rated as having low risk of bias	Lipids (mmol/L) Total cholesterol • 6 m (12 studies, n=576): -0.10 (-0.41, 0.20), p=NR, I^2=NR • 12 m (6 studies, n=430): 0.11 (-0.05, 0.27), p=NR, I^2=NR LDL-cholesterol • 6 m (15 studies, n=672): 0.02 (-0.09, 0.12), p=NR, I^2=NR. • 12 m (6 studies, n=429): 0.14 (-0.00, 0.28), p=NR, I^2=NR HDL-cholesterol • 6 m (16 studies, n=647): 0.06 (0.01, 0.10), p=NR, I^2=NR • 12 m (7 studies, n=458): 0.04 (-0.00, 0.08), p=NR, I^2=NR Triacylglycerols • 6 m (19 studies, n=860): -0.30 (0.43, -0.17), p=NR, I^2=NR • 12 m (7 studies, n=459): -0.32 (-0.51, -0.12), p=NR, I^2=NR Diabetes medication Number of persons who reduced medication • At 6 m (7 studies, n=240): 0.24 (0.12, 0.35), p=NR, I^2=NR • At 12 m (3 studies, n=148): 0.33 (–0.00, 0.66), p=NR, I^2=NR	Limited number of trials (30%) allowed participants to reduce their medication use which impeded ability to assess diabetes remission without diabetes medication. **Conclusions**: Moderate to low certainty evidence suggests participants adhering to LCDs for 6 m may experience greater rates of diabetes remission without adverse consequences compared with other diets commonly recommended for T2D management. These benefits are diminished at 12 m.

First author (year)	Methods	Included studies	Results of meta-analyses (WMD in change) (95% CI))	Limitations and study conclusions (as assessed by authors)
Silverii et al (2020) **Aim**: To assess if low carbohydrate diets are associated with long-term improvement in glycemic control and weight loss in people with T2D, and their cardiovascular and renal safety. **Countries**: Australia (8), Austria (1), Canada (2), China (3), Czech Republic (1), Israel (2), Japan (2), New Zealand (2), Spain (1), Sweden (3), UK (3), USA (9) **Funding source**: research performed as part of the institutional activity of the unit, with no specific funding. **Declarations of interest**: 4 authors received speaking fees and/or research grants and/or	**Search period**: Inception up to 1 March 2020 **Databases searched**: PubMed, Cochrane, Clinical Trials. gov, Embase **Language restrictions**: None specified **Inclusion criteria**: • RCTs (≥12 wks) in adults with T2D comparing LCD (≤45% TE from CHOs) with a CHO balanced diet (≥45% TE from CHOs) (HCD) • no other difference in treatment protocol between two arms • HbA1c reported at end of study for both treatment arms; • RCTs with wider inclusion criteria, if subgroups with T2D separately reported **Exclusion criteria**: none specified. **Outcome measures**: • Primary: HbA1c, BMI, creatinine, glomerular filtration rate • Secondary: body weight, total, HDL, LDL cholesterol, BP, QoL, adherence to prescribed diet Timepoints for outcome measurements: 3–4, 6–8, 12, 24 m **Statistical analysis**:	**Number of studies**: 37 (n=3301) **Study duration**: 3 to 48 m **Study population**: • Age range: 49.7 to 66.8 y • BMI: 21 to 38 kg/m^2 • Sex: NR • Ethnicity: NR • Medication: NR • Physical activity: NR **Intervention**: LCD (≤45% TE) • CHO intake ranged from 13 to 45% TE/20 to130 g/day **Comparator**: Balanced diet (≥45% TE) • CHO intake ranged between 45 and 65%. **Authors' evaluation**: Risk of bias: overall summary not provided. Publication bias: Not indicated	**Reported CHO intake** (mean): 31 studies reported CHO intakes at endpoint • LCD: 36% TE • HCD: 48.6% TE **Attrition rates**: no difference between groups **Outcomes**: HbA1c (%) • 3 m (22 studies, n=1239): -0.18 (-0.28 to -0.07), p=0.009, I^2=35% • 6 m (17 studies, n=1561): -0.19 (-0.40 to 0.01), p=0.07, I^2=58% • 12 m (16 studies, n=1561): -0.02 (-0.12 to 0.07), p=0.65, I^2=56% • 24 m (6 studies, n=742): (0.02 to 0.44), p=0.04, I^2=0% Weight (kg) • 3 m (20 studies, n=1157): -1.37 (-3.33 to 0.59), p=0.17, I^2=40% • 6 m (14 studies, n=1272): -0.54 (-2.42 to 1.35), p=0.58, I^2=0% • 12 m (14 studies, n=1408): 0.39 (-0.14 to 0.91), p=0.15, I^2=0% • 24 m (6 studies, n=888): 0.51 (-2.26 to 3.28), p=0.72, I^2=24%. Lipids (mmol/L) Total cholesterol	**Limitations**: Most trials relatively small, limiting precision of estimates of treatment effect. Most studies had short follow-up, limiting possibility of extending results to longer-term treatment. Many trials had methodological limitations, which introduce a possible bias. High heterogeneity detected for many outcomes. Possibility of selective reporting for some outcomes (such as renal safety) which could have produced an overestimation of safety of LCDs. **Conclusions**: LCDs may produce small short-term improvements in HbA1c and weight, which are not maintained in the long term. Data on their renal safety are insufficient.

First author (year)	Methods	Included studies	**Results of meta-analyses** (WMD in change) (95% CI))	**Limitations and study conclusions** (as assessed by authors)
consultancy fees from Astra Zeneca, Boehringer-Ingelheim, Bristol Myers, Eli-Lilly, Merck, Novo Nordisk, Sanofi, Squibb, Takeda. 3 authors, no conflicts of interest.	• Random effects model • Heterogeneity assessed using I^2 statistic • Subgroup analysis of trials comparing very low CHO diets (<26% TE/130g/day CHO) with standard diets (for HbA1c and BMI) **Study quality**: GRADE and Cochrane risk of bias tool. **Publication bias**: Funnel plot (for HbA1c)		• 3 m (17 studies, n=921): -3.08 (-7.51, 1.36); p=0.17, I^2=0% • 6 m (15 studies, n=1210): 4.64 (0.47, 8.81); p=0.03, I^2=0% • 12 m (15 studies, n=1357): 1.20 (-2.48, 4.88); p=0.52, I^2=9% • 24 m (5 studies, n=654): 6.74 (0.34, 13.14); p=0.04, I^2=0% <u>LDL-cholesterol</u> • 3 m (13 studies, n=691): 1.21 (-3.33, 5.76); p=0.60, I^2=0% • 6 m (14 studies, n=1244): 3.64 (-0.02, 7.30); p=0.05, I^2=0% • 12 m (13 studies, n=1295): 1.16 (-2.83, 5.16); p=0.57, I^2=33% • 24 m (5 studies, n=654): 5.33 (-0.44, 11.10); p=0.07, I^2=0% <u>HDL-cholesterol</u> • 3 m (17 studies, n=913): -1.63 (-3.14, -0.11); p=0.04, I^2=24% • 6 m (15 studies, n=1253): 0.14 (-1.24, 1.52); p=0.84, I^2=14% • 12 m (14 studies, n=1292): 1.24 (0.01, 2.46); p=0.05, I^2=7% • 24 m (5 studies, n=654): 2.04 (-3.33, 7.40); p=0.46, I^2=85	

First author (year)	Methods	Included studies	**Results of meta-analyses** (WMD in change) (95% CI))	**Limitations and study conclusions** (as assessed by authors)
McArdle et al (2019) **Aim**: To evaluate the impact of carbohydrate restriction on glycaemic control in adults with T2D **Countries**: Australia (5), Canada (1), Israel (3), Italy (1), Japan (2), Malaysia (1), New Zealand (2), Sweden (2), UK (3), US (5) **Funding source**: independent research supported by National Institute for Health Research & Health Education England **Declarations of interest**: 1 author received honoraria from Healthspan, Eli Lilly and NovoNordisk.	**Search period**: 1976 to April 2018 **Databases searched**: Medline, EMBASE, CINAHL. Databases of ongoing trials, Cochrane Library, DARE, dissertations, theses, other grey literature. **Language restrictions**: None. **Inclusion criteria**: • RCTs of adults with T2D comparing CHO restricted diet (not defined) to any control diet without CHO restriction • Minimum duration 8 wks and outcomes reported at ≥12 wks • Self-reported or measured CHO intake during or at end of intervention • HbA1c reported as an outcome **Exclusion criteria**: • Control diets that included CHO restriction in comparison to intervention diet **Outcome measures:** • Primary: HbA1c, body weight • Secondary: weight; lipid profile (not specified), BP **Statistical analysis:**	**Number of studies**: 25 (n=2132) **Study duration**: 3 to 48 m (12 to 208 wks) **Study population**: • Age range: 52 to 64 y • BMI: not reported • Sex: male and female (24 studies); female only (1 study) • Ethnicity: 4 studies, White/European (58 to 84%); 2 studies, African American (62 & 63%); 1 study, Malay (53%); 18 studies, not reported • Medication: not reported • Physical activity: not reported **Intervention**: CHO-restricted diet (not defined) **Comparator**: • Control diet without CHO restriction **Authors' evaluation**: Risk of bias: principal risk of bias due to either poor description of randomization sequence and allocation	**Reported CHO intake**: mean intakes ranged between 41 to 209g/d (median, 166g/d) in 13 studies that reported adherence to prescribed CHO intakes **Retention rates**: NR **Outcomes**: HbA1c (%) (25 studies, n=2132) • -0.09 (-0.27, 0.08), p=0.30, I^2=72%, Subgroup analysis based on prescribed CHO category • Very low vs high (8 studies, n=477): -0.13 (-0.34, 0.08), p=0.28, I^2=0% • Low vs high (5 studies all ≤6 months, n=239): -0.49 (-0.75, -0.23), p<0.001, I^2=0% Subgroup analysis of 13 studies that reported relative adherence to prescribed lower CHO diet (± 10%) • -0.06 (-0.15, 0.02), p=0.16, I^2=88% Weight change (kg) (23 studies, n=2018): • -0.13 (-0.33, 0.08), p=0.22, I^2=78% Subgroup analysis based on prescribed CHO category • Low vs high (5 studies all ≤6 months, n=239): -0.43 (-0.74, -0.12), p=0.006, I^2=24% Lipids:	**Limitations**: Lack of: • isocaloric study arms • adherence to study diet • standardisation of definitions relating to amounts of CHO intake • blinding to treatment allocation. Differences in: • baseline glycaemic control of participants • study protocols for adjustment of diabetes medication. Varied methods of dietary assessment and their inherent inaccuracies. Majority of studies did not report or adjust for physical activity level in analyses. Improvements in HbA1c may be related to reduction in energy intake and subsequent weight loss. **Conclusions:** No overall effect of CHO restriction on HbA1c or body weight. The evidence

First author (year)	Methods	Included studies	**Results of meta-analyses** (WMD in change) (95% CI))	**Limitations and study conclusions** (as assessed by authors)
	• MAs using random-effects model performed for primary outcomes: HbA1c and body weight • Heterogeneity assessed using I^2 statistic • Subgroup analysis according to categories of CHO intake (very low, low, moderate+) and adherence to study diet (±10% of prescribed CHO) **Study quality**: Cochrane risk of bias tool. **Publication bias**: not reported	concealment or no description of pre-study dietary intake ('other bias') Publication bias: Not reported	MAs not conducted for blood lipid outcomes which were reported in 17 studies: • 7 out of 17 studies reported significant differences between groups • Most commonly observed difference was a greater increase in HDL cholesterol in the lower CHO groups.	suggests short-term improvements in glycaemic control achieved by restriction of CHO intake to 50–130 g per day; however, little evidence to support recommending restriction of CHO intake for all people with T2D. Results raise important questions about long-term sustainability of such diets.

Table A4.2: Summary of network meta-analysis

Study	Methods	Included studies	Results	Limitations/ Comments
Neuenschwander et al (2019) **Aim**: To assess effects of different dietary approaches on blood lipid control (LDL cholesterol, HDL cholesterol and triglycerides) in adults with T2D **Countries**: North America (16), Asia (8), Australia and New Zealand (15), Europe (13) **Funding source**: German Federal Ministry of Health and Ministry of Innovation, Science, Research and Technology of the State North Rhine-Westphalia. **Declarations of interest**: None	**Search period**: Up to January 2018 **Databases searched**: Pubmed, CENTRAL **Language restrictions**: None **Inclusion criteria**: • RCTs comparing different dietary approaches in adults (≥18 y) with T2D; • Duration ≥3 m • Primary outcome, HbA1c; secondary outcome, defined FBG **Exclusion criteria**: • Studies including pregnant women and adults with T1D, abnormal glucose metabolism or chronic renal disease • Studies solely based on dietary approaches or single foods, using dietary supplements as placebo, exercise or medication co-intervention not applied to all groups, those based on very low energy diets (<600 kcal/day) **Outcome measures**: • LDL cholesterol, HDL cholesterol, triglycerides **Statistical analysis**: • Random-effects NMA	**Number of studies**: 52 (n=5360) **Duration**: 3 to 48 m **Study population**: • Mean age: 44 to 65 y • BMI: 23 (Asian population) to 40 kg/m^2 • Sex: male and female (48), female (1), NR (3) • Ethnicity: NR • Medication: not summarised • Physical activity: NR **Intervention**: • LCD (25% TE) • MCD (25 to 45% TE) • HPD (protein >20% TE; fat <35% TE) • LFD (fat <30% TE) • Low GI/GL • Vegetarian/vegan diet • Mediterranean dietary pattern • Paleolithic diet **Control**: • No or minimal intervention **Authors' evaluation:**	**Comparison**: Only results for LCD and MCD shown • LCD vs control • MCD vs control; MCD vs LCD **Dropouts**: not summarised **Reported CHO intake:** NR **Outcomes**: Mean difference (95% CI) <u>LDL cholesterol (mmol/)</u> • LCD vs control -0.05 (-0.25, 0.16) • MCD vs control -0.21 (-0.38, -0.05) • MCD vs LCD -0.17 (-0.36, 0.02) <u>HDL cholesterol (mmol/L)</u> • LCD vs control 0.06 (-0.01, 0.12) • MCD vs control 0.01 (-0.04, 0.06) • MCD vs LCD -0.05 (-0.11, 0.01) <u>Triglycerides (mmol/L)</u> • LCD vs control -0.36 (-0.62, -0.10) • MCD vs control -0.21 (-0.43, 0.00) • MCD vs LCD 0.15 (-0.09, 0.38) <u>Ranking of different diets</u>: most beneficial approach for management of diabetic dyslipidaemia (3 outcomes combined) was Mediterranean diet (SUCRA 79%), followed by the Palaeolithic (SUCRA 73%), LCD (SUCRA 62%) and MCD (SUCRA 61%). <u>Sensitivity analyses</u>: • excluding studies with high RoB: in general, confirmed results of main analysis	**Limitations**: • Study quality and indirect comparisons lowered confidence in estimates. • Adherence to dietary programme not accounted for in analyses. • Heterogeneous definition and overlap between different dietary approaches. • Not possible to assess potential mediating effect of energy restriction on results. • Information lacking on existing comorbidities and diabetes severity and data on medication intake differed between studies. Therefore, not possible to conduct sensitivity analyses

Study	Methods	Included studies	Results	Limitations/ Comments
	• Sensitivity analyses: excluding trials with high risk of bias, including only trials ≥ 12 m and including only trials of participants with a mean diabetes duration of ≥ 5 y • Univariate meta-regression: association between mean differences in weight change and changes in outcomes • Relative ranking of diets, distribution of ranking probabilities and SUCRA Study quality: Cochrane risk of bias tool to assess methodological quality GRADE, to assess credibility of evidence Publication bias: • Funnel plot if ≥10 studies available • Inference on risk for publication bias based on non-statistical considerations	**Risk of bias**: • 19 trials, low risk • 7 trials, high risk • 26 trials, moderate/unclear risk Credibility of evidence: • LDL and HDL: for significant associations, credibility of evidence mainly low. • Triacylglycerols: credibility of evidence low for the LCD compared to control, low GI/GL and LFD Publication bias: none detected.	• including only long-term trials (≥ 12 m): effects pointed to same directions • including only trials in participants with diabetes duration ≥ 5 y: stronger LDL reductions for vegetarian vs control diet. Meta-regression: positive trend between differences in weight change and changes in triglycerides (0.039 mmol/L higher per 1 kg mean difference in weight change (95% CI: 0.004, 0.073, p=0.03) but not for changes in LDL and HDL.	considering these aspects. **Conclusions:** Mediterranean diet most effective to manage diabetic dyslipidaemia. However, findings limited by low credibility of evidence.

Annex 5: Summaries of eligible 8 systematic reviews with meta-analyses and 1 network meta-analysis

Table A5.1: Summaries of systematic reviews with meta-analyses

Study	**Methods**	**Included studies**	**Results of meta-analyses** (weighted mean difference in change) (95% CI)	**Limitations and study conclusions** (assessed by authors)
van Zuuren et al (2018) **Aim**: To compare the effects of dietary carbohydrate restriction with fat restriction on markers of metabolic syndrome and quality of life in people with T2D. **Countries**: Australia (2), Europe (14), Israel (2), Japan (2), Mexico (1), US and Canada (15) **Funding source**: Supported by grants from the Dutch Diabetes Foundation and Sanofi **Declarations of interest:** None	**Search period**: To 21 March 2017 **Databases searched**: Medline, PubMed, Embase, Web of Science, Cochrane Library, CENTRAL, Emcare, Academic Search Premier, ScienceDirect, Latin American and Caribbean Health Science Information Database, Indice Bibliografico Espanol en Ciencias de Salud **Language restrictions**: None reported **Inclusion criteria:** • RCTs and CCTs comparing LCD (≤40% TE) with LFD (≤30% TE) ≥4 wks in adults (aged ≥18 y) with T2D • Data from crossover trials with washout of ≥4 wks between interventions. In absence of adequate wash-out period, data only included if able to extract data for 1st phase **Exclusion criteria:**	**Number of studies**: 36 (n=2161) **Study duration**: 4 wks to 7 y **Study population**: • Age range (mean): 32 to 65 y • BMI: NR • Sex: male (4), female (3), both (29) • Ethnicity: NR • Medication: insulin (5 trials), oral hypoglycaemic agents (25 trials), anti-hypertensive drugs (3 trials), lipid-lowering medications (10 trials). In 5 trials, anti-diabetic drugs discontinued or reduced; 5 trials did not provide details of medication; 2 trials, no medication use • Physical activity: 8 trials encouraged increase in physical activity	**Reported CHO intake**: NR **Retention rates**: NR **Outcomes**: <u>HbA1c (%)</u> • ≥16 to 26 wks: -0.26 (-0.50, -0.02), p=0.04, I^2=59% • >26 wks: -0.36 (-0.58, -0.14, p=0.001), I^2=0% • 2 y: 0.02 (-0.37, 0.41), p=0.93, I^2=13% <u>Weight (kg)</u> • ≥16 to 26 wks: -2.51 (-5.42, 0.40), p=0.09, I^2=88% • >26 wks: -0.19 (-1.65, 1.27), p=0.80, I^2=0% • 2 y: -0.14 (-1.64, 1.35), p=0.85, I^2=0% <u>Lipids (mmol/L)</u> <u>LDL-cholesterol</u> • ≥16 to 26 wks: 0.02 (-0.09, 0.13), p=0.75, I^2=0% • >26 wks: -0.07 (-0.23, 0.09), p=0.41, I^2=50% • 2 y: 0.06 (-0.08, 0.21), p=0.39, I^2=0%	**Limitations**: High degree of clinical and methodologic heterogeneity between included studies. Energy percentage of macronutrients in prescription diets differed considerably. Numerous other aspects differed considerably between studies including calorie content, exercise prescription, provision of food by study centre and reporting of actual food intake. Inconsistent methods of quantification and reporting of medication use precluded reliable statistical analyses of changes in drug doses. **Conclusions**: Low to moderate certainty of evidence that dietary CHO

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
	• Studies that included adults with other chronic diseases (except hypertension or CVD), any disease requiring hospital care • Studies that included those with an eating disorder or other disease re special dietary requirements **Outcome measures**: • Primary: HbA1c, whole blood and FPG and lipids (triacylglycerol, LDL-c, HDL-c) • Secondary: weight, BMI, waist circumference, BP, QoL **Statistical analysis**: • Random-effects model • Heterogeneity assessed using I^2 statistic (I^2>50% indicative of substantial heterogeneity) • Several sensitivity analyses to explore sources of heterogeneity • Repeated analyses using fixed-effects model in MAs with between study heterogeneity **Study quality**: GRADE (to assess certainty of evidence) and Cochrane risk of bias tool. **Publication bias**: Paucity of studies evaluating any of the outcomes at same timepoints did not permit assessment.	**Intervention**: **LCD** (CHO ≤40% TE) • Ranged from 10 to 40% TE/<20 to <130 g **Comparator**: LFD (≤30% TE) • Fat intake ranged from 10 to 30% TE • CHO intake ranged from 45 to 70% TE **Authors' evaluation**: Risk of bias RCTs (n=33): 19, high risk; 14, unclear risk CCTs (n=3): moderate to serious	HDL-cholesterol • ≥16 to 26 wks: 0.09 (-0.03, 0.22), p=0.13, I^2=91% • >26 wks: 0.11 (0.05, 0.18), p<0.0007, I^2=66% • 2 y: 0.12 (0.07, 0.17), p<0.00004, I^2=0% Triacylglycerols • ≥16 to 26 wks: -0.22 (-0.37, -0.08), p=0.002, I^2=41% • >26 wks: -0.25 (-0.47, -0.04), p=0.02, I^2=73% • 2 y: -0.19 (-0.32, -0.05), p=0.007, I^2=0%	restriction to maximum of 40% yields slightly better metabolic control of uncertain clinical importance than reduction in fat to a maximum of 30% in people with T2D.

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
Korsmo-Haugen et al (2018) **Aim**: To compare the effects of low carbohydrate diets on body weight, glycaemic control, lipid profile and BP with those observed on higher carbohydrate diets in adults with T2D **Countries**: Australia (5), Europe (5), Israel (3), Japan (1), New Zealand (1), North America (8) **Funding source**: No particular funding received **Declarations of interest**: None	**Search period**: 1983 to 31 January 2016 **Databases searched**: Medline, Embase, CINAHL, CENTRAL, Food Science Source and SweMed **Language restrictions**: English, Danish, Norwegian, Swedish **Inclusion criteria**: • RCTs with more than 3 m duration comparing diet below to a diet above 40% TE from CHO • Comorbidities accepted but studies including individuals with impaired glucose tolerance and/or T1D only included if separate data provided for T2D individuals **Exclusion criteria**: • Complex interventions consisting of elements with potential to interfere with effect of dietary interventions (such as parenteral administration or promotion of physical activity) **Outcome measures**: • Weight, HbA1c, lipids (triacylglycerol, total cholesterol, LDL-c, HDL-c), BP, compliance to dietary intervention **Statistical analysis**:	**Number of studies**: 23 (n=2178) **Study duration**: 3 m to >3 y **Study population**: • Age range: NR • BMI: NR • Sex: NR • Ethnicity: NR • Medication: insulin therapy (12 trials), anti-hypertensive drugs (8 trials), lipid-lowering drugs (10 trials) and oral hypoglycaemic agents such as metformin (10), sulfonylurea (10), thiazolidinedione (4) • Physical activity: several trials promoted general recommendations for physical activity **Intervention**: LCD (CHO <40% TE) • Ranged from 5 to 40% TE **Comparator**: Variety of diets: LFD (n=8), standard diabetes care (n=4), HCD (n=3), LPD (n=1), Med (n=2), HCD/LFD (n=2), High wheat fibre (n=1), Low GI (n=2), High GI (n=1)	**Reported CHO intake** (mean): • 9/18 studies CHO intakes in LCD were 5% TE within prescribed intakes • 7/9 trials that observed low compliance, participants were on VLCD (CHO intakes of 5 to 22% TE) **Attrition rates**: LCD vs HCD • No detectable difference in attrition rates between diets: RR=1.08 (95% CI, 0.92, 1.27; I^2=0%) **Outcomes**: <u>HbA1c (%)</u> • 3 to 6 m: -0.17 (-0.27, -0.08), p=NR, I^2=0% • >12 m: 0.00 (-0.10, 0.09), p=NR, I^2=0% <u>Weight (kg)</u> • 3 to 6 m: -0.87 (-1.88, 0.15), p=NR, I^2=33%, • >12 m: 0.14 (-0.29, 0.57), p=NR, I^2=0% Sensitivity analyses showed less difference between LCDs and HCDs in studies with low RoB than in those with high RoB. <u>Lipids (mmol/L)</u> <u>Total cholesterol</u> • 3 to 6 m: -0.06 (-0.41, -0.30); p=NR, I^2=57%, • >12 m: 0.07 (-0.04, 0.19); p=NR, I^2=23%	**Limitations**: Ability to follow diet with very low CHO content was generally poor. Changes in medications over time may have blurred effects of differences in diet composition. **Conclusions**: The proportion of daily energy provided by CHO intake is not an important determinant of response to dietary management, especially when considering longer-term trials.

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
	• Random effects model • Lipid profile qualitatively evaluated • Heterogeneity assessed using I^2 statistic (I^2>50% or value of Cochrane Q test <0.1 associated with heterogeneity) and subgroup analyses to explore possible reasons for heterogeneity • Post hoc subgroup and sensitivity analyses to explore impact of study duration (6 vs 12 m), varying CHO content (VLCD 21 to 70 g vs LCD 30 to 40% TE) and risk of bias (low vs high) **Study quality**: GRADE and Cochrane risk of bias tool. **Publication bias**: Funnel plot	• CHO intake ranged between 42 and 65%. **Authors' evaluation**: Risk of bias: Overall, 3 studies classified as low risk, 10 as high risk and 10 as unclear risk Publication bias: Not indicated	LDL-cholesterol • 3 to 6 m: -0.08 (-0.29, 0.14); p=NR, I^2=50%, • >12 m: 0.03 (-0.10, 0.16); p=NR, I^2=51% HDL-cholesterol • 3 to 6 m: -0.01 (-0.07, 0.04); p=NR, I^2=15% • >12 m: 0.06 (-0.01, 0.13);p=NR, I^2=71% Triacylglycerols • 3 to 6 m: -0.18 (-0.36,0.00); p=NR, I^2=20% • >12 m: -0.10 (-0.23, 0.03); p=NR, I^2=61%	

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
Sainsbury et al (2018) **Aim**: To compare effectiveness of carbohydrate-restricted diets with high carbohydrate diets on glycaemic control in adults with T2D **Countries**: Austria (1), Australia (6), Canada (2), Czech Republic (1), Israel (2), Japan (2), New Zealand (1), Sweden (1), UK (2), US (7) **Funding source**: Did not receive specific grant from funding agencies in public, commercial or not-for-profit sectors **Declarations of interest**: None	**Search period**: 1 January 1980 to 31 August 2016 **Databases searched**: Medline, Embase, CINAHL, Global Health, Cochrane **Language restrictions**: English **Inclusion criteria**: • RCTs comparing CHO-restricted diet (≤45% TE) to HCD (>45% TE) for glycaemic control in adults (≥18 y) with T1D or T2D • Studies had to report on change in HbA1c and minimum duration of 3 m • Studies of individuals with and without diabetes only included if ≥80% had diabetes or if subgroup analysis for this group **Exclusion criteria**: • 1 intervention group included a non-dietary weight loss component (such as physical activity advice, pharmaceutical intervention) while other group did not • Trials with meal replacement drinks or enteral feeds • Studies of prediabetes, gestational diabetes, pregnant or lactating women	**Number of studies**: 25 (n=2412) **Study duration**: 3 to 24 m **Study population**: • Age range: 52 to 63 y • BMI: 25.8 to 38.1 kg/m^2 (median, 36.7) • Sex: male and female • Ethnicity: NR • Medication: majority on diabetes medication and/or insulin (1 study, diet treatment only); 11 studies allowed medication adjustments during intervention, with 5 reporting that they accounted for this in analysis • Physical activity: 15 studies included advice (to maintain or increase level) **Intervention**: CHO-restricted diet (≤45% TE) • LCD <130 g or <26% TE) (10 studies) • MCD (130 to 225 g or 26 to 45% TE) (15 studies) (4 studies increased % of protein, 6 increased % of fat,	**Reported CHO intake**: NR **Retention rates**: • 3 to 6 m (n=10): >70% • 12 to 24 m: 50 to 69% (n=6); ≥70% (n=8) **Outcomes**: <u>HbA1c (%)</u> • 3 m: -0.19 (-0.33, -0.05), p=0.008, I^2=28% • 6 m: -0.15 (-0.31, 0.02), p=0.09, I^2=50% • 12 m: -0.09 (-0.21, 0.03), p=0.12, I^2=16% • 24 m: -0.11 (-0.38, 0.15), p=NR, I^2=NR <u>Weight change (kg)</u> • 3 m: -1.08 (-1.93, -0.23), p=0.01, I^2=69% • 6 m: -0.14 (-0.94 to 0.65), p=0.72, I^2=48% • 12 m: -0.43 (-0.93, 0.07), p=0.09, I^2=0% <u>Lipids</u> • 3 to 6 m: no change or small reductions in total cholesterol and LDL-c on both CHO-restricted diet and HCD. Greater increase in HDL-c for CHO-restricted diet in 9/20 studies with 3 reporting significant difference between groups	**Limitations**: Due to high risk of performance and detection bias and inconsistency in estimates of effect across studies, the evidence of HbA1c change was graded low quality High variability in methods of analysis across studies CHO quantity based on prescribed rather than actual intake Did not consider effect that altering fat and protein proportions may have had on outcomes **Conclusions:** Over the short term (3 to 6 m) CHO-restricted diets (≤45% TE) produce greater reductions in HbA1c than HCD (>45% TE). These effects primarily driven by LCDs (<26% TE) with no significant difference between MCDs (26 to 45% TE) and HCDs. The short-term glycaemic improvements on LCDs appear to be due to weight loss with no significant

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
	Outcome measures: • Primary: HbA1c • Secondary: weight; lipid profile (triacylglycerol, total cholesterol, LDL-cholesterol, HDL-cholesterol) **Statistical analysis:** • Random-effects model to estimate HbA1c change at 3, 6, 12, 24 m. Subgroup analysis conducted at each time-point to test effect of different levels of CHO restriction on HbA1c • Lipid profile qualitatively evaluated • Heterogeneity assessed using I^2 statistic **Study quality**: GRADE and Cochrane risk of bias tool. **Publication bias**: Funnel plot and Egger's test	4 increased % of both protein and fat as proportion of TE, 14 studies isocaloric.) **Comparator**: • HCD (>225 g or >45% TE) **Authors' evaluation**: Risk of bias: Overall 9 studies classified as being low risk, 7 at high risk and 9 at unclear risk Publication bias: Present at 3 m (p=0.005) but not at 6 m (p=0.125) or 12 m (p=0.052). Not tested at 24 m (n=3)	• 12 to 24 m: 6 studies reported significantly greater increase in HDL-c and 5 reported significantly greater reductions in triacylglycerols for CHO-restricted diet compared with HC diet.	difference in HbA1c change between diets when restricted to studies with equal weight loss.

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
Huntriss et al (2018) **Aim**: To evaluate the clinical effect of a low carbohydrate diet in the management of T2D **Countries**: NR **Funding source**: Completed within a National Institute of Health Research funded Masters in Clinical Research **Declarations of interest**: None	**Search period**: until June 2016 **Databases searched**: Medline, Embase, CINAHL, Cochrane, ISRCTN, ProQuest, opengrey.eu. Reference lists of selected papers **Language restrictions**: English **Inclusion criteria**: • RCTs in adults aged: ≥18 y with T2D • LCD group must have achieved lower CHO intake than control group • Control group usual care (on variety of diets) **Exclusion criteria**: • Studies that enrolled individuals with T1D, pre-diabetes or included pregnant women **Outcome measures**: • Primary: HbA1c • Secondary: Change in diabetes medication, weight, total cholesterol, LDL-c, HDL-c, triacylglycerol, BP, dietary adherence **Statistical analysis**: • Random-effects model • MA performed for change in each outcome at 1 y	**Number of studies**: 18 (n=2204) **Study duration**: 12 wks to 4 y **Study population**: • Mean age: NR • BMI: NR • Sex: NR • Ethnicity: NR • Medication: Participants in 14/18 studies on diabetes medication; 2 studies did not include participants on medication; 2 did not report medication changes • Physical activity: NR **Intervention:** • CHO: <20 to 70 g/d /14 to 52% TE • All authors described intervention as low CHO • 10 studies prescribed LCD (<130 g/d or <26% TE) • 5 prescribed MCD (130 to 225 g/d or 26 to 45% TE) • 1 prescribed HCD (>225 g/d or 45% TE) • 1 prescribed up to 50% TE from CHOs **Comparator**:	**Dropout**: NR **Reported CHO intake** (mean): 106 g/d **Outcomes** (1 y) HbA1c (%) • -0.28% (-0.53, -0.02), p=0.03, I^2=54% Body weight (kg): 0.28 (-1.37, 1.92), p=0.74, I^2=75% Blood lipids (mmol/L) Total cholesterol: • -0.08 (-0.23, 0.08), p=0.35, I^2=60% LDL-c • 0.05 (-0.10, 0.19), p=0.54, I^2=0% HDL-c • 0.06 (0.04, 0.09), p<0.00001, I^2=1% Triacylglycerols • -0.24 (-0.35, -0.13,) p<0.0001, I^2=0% Diabetes medication: Out of 14 studies, 9 reported statistically significant reduction in diabetes medication in LCD group (p≤0.05). Dietary adherence: 12/18 trials reported CHO intake at trial end in LCD. Two reported that they achieved prescribed intake in the intervention arm, 1 that prescribed LCD and 1 that prescribed up to and including HCD.	**Limitations**: Varied CHO prescription across studies Lack of blinding of participants and study personnel True effect of LCD group on HbA1c could not be observed due to medication adjustments Study design heterogeneity present Some studies prescribed lower calorie allowance to control group Several studies provided insufficient information and could not be included in the MAs, limiting number of studies and participants that could be included in pooled analysis **Conclusions**: Statistically significant superiority of LCD in improving HbA1c, HDL-c, triacylglycerol at 1 y and in reducing diabetes medication. No difference in

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
	• Studies <48 wks or with marked design heterogeneity not included in MA **Study quality**: Assessed for risk of bias using Cochrane Risk of Bias tool **Publication bias**: Not assessed	Usual care, which included variety of diets • CHO: 50 to 60% TE • Fat: ≤30% TE **Authors' evaluation**: Risk of bias: 15/18 studies at high RoB in 1 or more of the 6 criteria [random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment), incomplete outcome data, selective reporting. 15/18 studies at high risk of performance bias.		weight loss, total cholesterol or LDL-c at 1 y. Reducing CHO intake may promote favourable health outcomes in management of T2D in context of a healthy diet.

Study	Methods	Included studies	**Results of meta-analyses** (weighted mean difference in change) (95% CI)	**Limitations and study conclusions** (assessed by authors)
Snorgaard et al (2017) **Aim**: Effect of dietary carbohydrate restriction compared with recommended diet containing 45 to 60% carbohydrate in people with T2D. **Countries**: Australia (2), Canada (1), Israel (1), Japan (1), New Zealand (1), Sweden (1), US (3) **Funding source**: Danish Health Authority **Declarations of interest**: A Astrup, member of advisory boards/consultant for: Lucozade Ribena Suntory, UK; McCain Foods Ltd, US; McDonalds, US; Nestle Research, Switzerland; Swedish Dairy, Weight Watchers, US.	**Search period**: January 2004 to October 2014 **Databases searched**: Embase, Medline, Cochrane Library **Language restrictions**: English and Scandinavian languages **Inclusion criteria**: • RCTs comparing CHO restriction (<45% TE) to 45 to 60% CHO diet in individuals with T2D • CHO restriction could be combined with higher intakes of fat, protein, or both **Exclusion criteria**: • Interventions aimed at also changing GI of diet **Outcome measures**: • Primary: HbA1c and BMI ≥1 y • Secondary: HbA1c and BMI (or weight) before 1 y, LDL-c, QoL, dropout rates **Statistical analysis**: NR **Study quality**: GRADE and AMSTAR Risk of bias assessed using Cochrane Risk of Bias tool **Publication bias**: Not assessed	**Number of studies**: 10 (n=1376) **Study duration**: 3 to 24 m **Study population**: • Age (mean): 58 y • Sex: 49% male • BMI (mean): 26 to 37 kg/m^2 • Ethnicity: NR • Medication: Reports on glucose-lowering medication available in 7 studies • Physical activity: 5 trials advised an increase in daily physical activity equally in both groups **Intervention**: • LCD: CHO <45% TE • Prescribed CHO intake (%): average predefined target 25% TE (range 14 to 40%) **Comparator**: • Recommended diet containing 45 to 60% CHO (HCD) **Authors' evaluation**: Risk of bias: overall risk, low to moderate	**Dropout**: • RR=1.13 (0.94, 1.37), I^2=0% **Reported CHO intake** (mean): • 3 or 6 m: 30% (range 14 to 45%) • 1 y: 38% (range 27 to 45%) • 2 y: increased further compared to 1 y (42 to 48% and 27 to 31%) or remained high (45%) **Outcomes**: HbA1c (%) • 3 or 6 m: -0.34 (-0.06, -0.63), p=0.02, I^2=74% • ≥1 y: 0.04 (-0.04, 0.13), p=0.29, I^2=0% Weight (kg) • <1 y: 0.00 (-1.03, 1.02), p=NR, I^2=NR • ≥1 y: 0.2 (-0.97, 1.36), p=NR, I^2=NR LDL-cholesterol (mmol/L)) • <1y: 0.04% (-0.06, 0.13), p=NR, I^2=NR • ≥1y: -0.01 (-0.1, 0.07), p=NR, I^2=NR Diabetes medication • 3 or 6 m: medication reduced in LCD compared to control • 1 y: numerically lower in LCD group	**Limitations**: Changes in glucose medication and variability in adherence to diet probably main factors modifying effect of LCD on glycaemic control. Other factors potentially contributing to heterogeneity of results: duration and intensity of intervention, CHO and total daily calorie intake in LCD and HCD groups, GI of CHOs, fat and protein intake, baseline HbA1c. **Conclusions**: CHO restriction (TE% < 45%) has greater effect on glycaemic control than HCD in short term. Magnitude of effect correlated to CHO intake: the greater the restriction, the greater the glucose lowering. In the long term, glucose-lowering effect of LDC and HCD similar. Isocaloric LCD and HCD had similar effects on weight and LDL-c.

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
Meng et al (2017) **Aim**: To evaluate overall effect of low carbohydrate diet on weight loss, blood glucose, and blood lipid concentrations in diabetic patients. **Countries**: Australia (1), Israel (1), Japan (1), Sweden (1), UK (1), US (4) **Funding source**: National Natural Science Foundation of China **Declarations of interest**: None	**Search period**: To January 2017 **Databases searched**: Medline, Embase, Cochrane Library **Language restrictions**: None **Inclusion criteria**: • RCTs in individuals with T2D • LCD: CHO <130 g/d or 26% TE • Control: normal or HCD • Studies reporting change in weight, FPG, HbA1c, total cholesterol, triacylglycerol, HDL-c, LDL-c **Exclusion criteria**: NR **Outcome measures**: • Primary: body weight • Secondary: HbA1c, FPG, total cholesterol, triacylglycerol, HDL-c, LDL-c **Statistical analysis**: Heterogeneity assessed using Q tests and I^2 statistics: p<0.1 or I^2>50% considered to represent significant heterogeneity and random-effects model used; otherwise fixed-effects model. **Study quality**: Modified Jadad scale. Random sequence generation, allocation concealment, double blinding, withdrawals and dropouts	**Number of studies**: 9 (n=734) **Study duration**: 3 to 24 m **Study population**: • Mean age: NR • Sex: NR • BMI: NR • Ethnicity: NR • Medication: NR • Physical activity: NR **Intervention**: • LCD: CHO <130 g/d or 26% TE • CHO intake <20 to 130 g/d or 5 to 20% TE **Comparator**: • Normal or HCD • CHO intake 45 to 60% TE (unclear in 3 studies) **Authors' evaluation**: Study quality: 5/9 studies considered to be of high quality (modified Jadad score ≥4) Publication bias: No evidence of publication bias	**Dropout**: NR **Reported CHO intake**: NR **Outcomes** Weight (units NR) • <1y (n=5): -1.18 (-2.32, -0.04); p=NR, I^2=55.9% • >1y (n=3): -0.24 (-2.18, 1.7); p=NR, I^2=0% HbA1c (units NR) • -0.44 (-0.61, -0.26); p=0.00, I^2=19.6% Fasting plasma glucose • -0.05 (-0.58, 0.47); p=0.84, I^2=0%; Blood lipids (mmol/L) Triacylglycerol • -0.33 (-0.45, -0.21); p=0.00, I^2=0% HDL-cholesterol • 0.07 (0.03, 0.11); p=0.00, I^2=40.6%; LDL-cholesterol • 0.04 (-0.08, 0.16); p=0.53, I^2=0.0% Total cholesterol • 0.06 (-0.08, 0.21); p=0.33, I^2=0.0%	**Limitations**: Only 5 studies considered to be of high quality. CHO intake in LCD ranged from 5% to 20% of daily energy. **Conclusions**: Results suggest beneficial effect of LCD on glucose control, triacylglycerols and HDL-c in adults with T2D but no significant effect on long term weight loss, total cholesterol or LDL-c.

Study	**Methods**	**Included studies**	**Results of meta-analyses** (weighted mean difference in change) (95% CI)	**Limitations and study conclusions** (assessed by authors)
	evaluated. Each study received score from 0 to 7; a score of > 4 considered to be of high quality. **Publication bias**: Funnel plots and Egger linear regression test			

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
Fan et al (2016) **Aim**: To evaluate the effect of low carbohydrate diets on weight reduction, glycaemic control and lipid profile in individuals with T2D **Countries**: Israel (1), Italy (1), Japan (1), Sweden (2), UK (1), US (4) **Funding source**: NR **Declarations of interest:** None	**Search period**: Inception until 30 May 2014 **Databases searched**: PubMed, Medline, Embase, Cochrane Library **Language restrictions**: None **Inclusion criteria**: • RCTs in adults aged ≥18 y with T2D • 1 group received LCD (maximum CHO intake of 130 g/d with any other type of diet) **Exclusion criteria**: • Participants aged <18 y or with T1D • Treatment allocation not random • Did not report data for at least 1 of the clinical outcomes of interest **Outcome measures** • Weight change, HbA1c, total cholesterol, HDL-c, LDL-c, triacylglycerol **Statistical analysis**: • Statistical heterogeneity assessed by I^2 statistic. When heterogeneity confirmed ($p<0.10$, I^2 >50%) random-effects method used; otherwise fixed-effects model used • Sensitivity analyses: to explore potential sources of heterogeneity and influence of various exclusion criteria on overall result	**Number of studies**: 10 (n=1080) **Study duration**: 3 m to 4 y **Study population**: • Mean age: NR • Sex: NR • BMI: NR • Ethnicity: NR • Medication: NR • Physical activity: NR **Intervention**: • LCD: 20-50% TE or 20-130 g/d **Comparator:** Variety of diets including: • Conventional CHO – 50 to 60% TE • HCD CHO - 60% TE • ADA (≥150 g/d CHO) • LFD -25 to ≤30% TE from fat (CHO intake not reported in 5 studies) **Authors' evaluation**: Study quality: All studies considered methodologically good. Jadad quality scores ranged from 3 to 5 points (out of maximum of 5), except 1 study with a score of 1.	**Dropout**: NR **Reported CHO intake**: NR **Outcomes**: Weight (kg): unclear HbA1c (%) • -0.33 (-0.51, -0.15); $p<0.001$, I^2=88.4% Blood lipids (mmol/L) Triacylglycerol • -0.28 (0.39, -0.17); p<0.001 HDL-cholesterol • 0.09 (0.04, 0.14); p<0.001 LDL-cholesterol • -0.027 (-0.11, 0.05); p=0.5 Total cholesterol • 0.05 (-0.14, 0.25); p=0.6 Sensitivity analyses: exclusion of any single study did not materially alter overall result.	**Limitations**: Significant confounders in performing MA of such varied interventions and publication bias and residual confounding may have existed. Diets different in composition, baseline, duration of studies. Difficult to distinguish effects of individual nutritional component. Lack of long-term follow-up data. Many studies did not provide information on exercise which can have a significant effect on weight loss and serum glucose. Very few studies performed ITT analysis. **Conclusions:** Differences on weight, HbA1c and lipids changes over the long-term comparing a LCD with other diets.

Study	**Methods**	**Included studies**	**Results of meta-analyses** (weighted mean difference in change) (95% CI)	**Limitations and study conclusions** (assessed by authors)
	Study quality: Jadad scale (randomisation, blinding and description of withdrawals and dropouts were evaluated. A cut-off score of 3 used to indicate high quality studies) Publication bias: Funnel plots, Egger's test and Begg's test	Publication bias: NR		

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
Naude et al (2014) **Aim**: To compare effects of low carbohydrate and isoenergetic balanced weight loss diets in overweight and obese adults. **Countries**: Australia (3), New Zealand (1), Sweden (1) **Funding source**: Not stated **Declarations of interest**: None	**Search period**: 1966 to 19 March 2014 **Databases searched**: Medline, Embase, Cochrane **Language restrictions**: English **Inclusion criteria**: • RCTs in overweight individuals with diabetes, glucose intolerance or insulin resistance, CVD conditions or risk factors • Provided macronutrient goals as TE or could be calculated as % of TE for both groups • Intervention: 2 main variants of low CHO weight loss diets: (a) High fat variant (HFV) – LCD (<45% TE), high fat (>35% TE), high protein diet (>20% TE) or (b) high protein variant (HPV) – LCD (<45% TE), recommended fat (25 to 35% TE), high protein diet • Control diets: balanced weight loss plans with similar prescribed energy content as intervention diet **Exclusion criteria**: • RCTs <n=10 per group or duration <12 wk • Aged <18 y or pregnant/lactating women	**Number of studies**: 5 (n=720) **Study duration**: 3 to 26 m **Study population**: • Age: 30 to 78 y • Sex: Male and female • BMI: >30 kg/m^2 • Ethnicity: NR • Medication: excluded studies with this component • Physical activity: excluded studies with this component **Intervention**: • CHO: 20% TE (1 study) or 40% TE (4 studies) • Fat: 30% TE (1 study) or 30% TE (4 studies) • Protein: 30% TE **Comparator:** • CHO: 55 to 60% TE • Fat: 25 to 30% TE • Protein: 10 to 15% TE **Authors' evaluation**: Study quality: Presence of risk of selection, performance and attrition bias in most included trials were primary reasons for the	**Dropout**: Ranged from 0 to 21% • 1 study: 0% in both groups • 3 studies: similar in both groups (9, 15 and 21%) • 1 study: 8% in LCD and 5.5% in control **Reported CHO intake**: NR. **Outcomes**: Weight (kg) • 3 to 6 m: 0.82 (-1.25, 2.90), p=0.44, I^2=0% • 12 to 24 m: 0.91 (-2.08, 3.89), p=0.55, I^2=33% HbA1c (%) • 3 to 6 m: 0.19 (-0.0, 0.39), p=0.05, I^2=0% • 12 to 24 m: 0.01 (-0.28, 0.3), p=0.95, I^2=0% Blood lipids (mmol/L) Triacylglycerol • 3 to 6 m: -0.20 (-0.45, 0.05), p=0.12, I^2=0% • 12 to 24 m: -0.08 (-0.43, 0.26), p=0.63, I^2=0% HDL-c • 3 to 6 m: -0.01 (-0.05, 0.04, p=0.71), I^2=0% • 12 to 24 m: 0.00 (-0.09, 0.08), p=0.91, I^2=26%	**Limitations**: Risk of bias or lack of power or both in many included trials. Adherence to macronutrient goals not optimal. Interpretation of many weight loss trials limited by lack of blinded ascertainment of outcome, small samples, large loss to follow-up, potentially limited generalisability and lack of data on adherence to assigned diets. **Conclusions:** Little/no difference in changes in weight and CVD and diabetes risk factors with LCDs compared to isoenergetic balanced weight loss diets. Weight loss result of reduction in total dietary energy intake rather than manipulation of macronutrients.

Study	Methods	Included studies	Results of meta-analyses (weighted mean difference in change) (95% CI)	Limitations and study conclusions (assessed by authors)
	• Treatment and control diets not adequately defined • Diets combined with any other intervention (such as physical activity, pharmacological) • Intervention focused on energy restriction • Substantial disparity in energy intake (>500 KJ) between groups **Outcome measures**: • Weight loss, BMI, HbA1c, total cholesterol, HDL-c, LDL-c, triacylglycerol **Statistical analysis**: • Random-effects model Study quality: GRADE (used to express quality of evidence and magnitude of effect. For large effects and moderate quality evidence, used the word 'probably'; for low quality, used the word 'may') Cochrane risk of bias tool. Publication bias: Assessed with funnel plots when ≥10 studies per outcome	moderate grade of evidence in most outcomes. For weight loss at 3 to 6 m and 1 to 2 y follow-up, imprecision of the effect estimates resulted in further downgrading to low quality evidence.	LDL-c • 3 to 6 m: 0.06 (-0.11, 0.23), p=0.50, I^2=25% • 12 to 24 m: 0.10 (-0.06, 0.27), p=0.23, I^2=0% Total cholesterol • 3 to 6 m: 0.04 (-0.21, 0.30), p=0.73, I^2=43% • 12 to 24 m: 0.10 (-0.12, 0.31), p=0.37, I^2=9%	

Table A5.2: Summary of network meta-analysis

Study	Methods	Included studies	Results (mean difference) (95% CI)	Limitations/ Comments
Schwingshackl et al (2018) **Aim**: Comparative efficacy of different dietary approaches on glycaemic control in adults with T2D **Countries**: Asia (8), Australia (13), Canada (4), Europe (14), New Zealand (3), US (14) **Funding source**: NR **Declarations of interest**: No competing interests	**Search period**: Up to July 2017 **Databases searched**: PubMed, Cochrane Library, Google Scholar **Language restrictions**: None **Inclusion criteria**: • RCTs comparing different dietary approaches in adults (≥18 y) with T2D; intervention period ≥12 wks • Primary outcome, HbA1c; secondary outcome, defined FBG **Exclusion criteria**: • Studies including pregnant women and patients with abnormal glucose metabolism • Studies solely based on dietary approaches or single foods, using dietary supplements as placebo, exercise or medication co-intervention not applied to all groups, those based on very low energy diets (<600 kcal/day) **Outcome measures**: • Primary: HbA1c • Secondary: Defined FBG **Statistical analysis**: • Random-effects NMA	**Number of studies**: 56 (n=4937) **Duration**: 3 to 48 m **Study population**: • Mean age: 44 to 67 y • BMI: 25 to 43 kg/m^2 • Sex: NR • Ethnicity: NR • Medication: NR • Physical activity: NR **Intervention**: • LCD (CHO <25% TE; high intake protein/fat) • MCD (CHO 25 to 45% TE; 10 to 20% protein intake) • HPD (protein >20% TE; fat <35% TE) • LFD (fat <30% TE; high intake cereals/grains; protein 10 to 25% TE) • Low GI/GL • Vegetarian/vegan diet • Mediterranean dietary pattern • Paleolithic diet **Control**: • No or minimal intervention **Authors' evaluation:**	**Comparison**: Only results for LCD and MCD reported here • LCD vs control/MCD/LFD/HPD • MCD vs control/LFD/HPD **Dropout**: NR **Reported CHO intake:** NR **Outcomes** <u>HbA1c (%)</u> (contribution to estimate of direct/indirect comparisons %) • LCD vs control -0.82 (-1.11, -0.53) (0/100) • LCD vs MCD -0.23 (-0.50, 0.04) (23/77) • LCD vs LFD -0.35 (-0.56, -0.14) (83/17) • LCD vs HPD -0.33 (-0.61, -0.05) (0/100) • MCD vs control -0.59 (-0.85, -0.32) (19/81) • MCD vs LFD -0.12 (-0.31, 0.08) (57/43) • MCD vs HPD -0.10 (-0.37, 0.17) (0/100) <u>FBG (mmol/L)</u> (contribution to estimate of direct/ indirect comparisons %) • LCD vs control -1.23 (-1.91, -0.55) (0/100) • LCD vs MCD -0.03 (-0.68, 0.62) (20/80) • LCD vs LFD -0.24 (-0.82, 0.35) (57/43) • LCD vs HPD -0.16 (-0.88, 0.57) (0/100) • MCD vs control -1.20 (-1.69, -0.71) (25/75) • MCD vs LFD -0.20 (-0.56, 0.15) (61/39)	**Limitations**: Number and quality of studies available. Analyses based on original intended randomised design not on adherence. Adherence to dietary programme not accounted for in analyses. Heterogeneous definition and overlap between different dietary approaches. Statistical inconsistencies. Significant differences in LCD compared to other dietary approaches for study duration, sample size and patients' age. **Conclusions:** LCD diets more effective in HbA1c reduction in short term compared to other diets but no

Study	Methods	Included studies	Results (mean difference) (95% CI)	Limitations/ Comments
	• Subgroup analyses: study duration (≥12 vs <12 m), sample size (≥100 vs <100), age (≥60 vs <60 y) • Sensitivity analyses of studies at low RoB and excluding RoB trials • Relative ranking of diets, distribution of ranking probabilities and surface under cumulative ranking curves (SUCRA) • Meta-regression analysis: association between HbA1c and mean differences in weight change Study quality: GRADE, to assess credibility of evidence; Cochrane risk of bias tool to assess methodological quality. Publication bias: assessed primarily on non-statistical considerations and funnel plot	**Risk of bias**: • 21 trials, low risk • 7 trials, high risk • 28 trials, moderate/unclear risk Credibility of evidence rated very low for LCD vs LFD, LCD vs MCD, LCD vs HPD Publication bias: comparison adjusted funnel plots for both outcomes slightly asymmetric when LFD vs other dietary approaches.	• MCD vs HPD -0.13 (-0.69, 0.44) (0/100) Ranking of different diets: LCD best dietary approach for reducing HbA1c (SUCRA, 84%); MCD ranked 6th (SUCRA, 46%). Subgroup analyses: LCD more effective in reducing HbA1c in the shorter term (<12 m), in smaller size studies and including patients ≥60 y. Meta-regression: mean reduction in HbA1c significantly related to mean difference in weight change between different dietary approaches.	superiority observed in the longer term. Mediterranean diet seems to be most effective and efficacious to improve glycaemic control in T2D individuals. These findings need to be seen in light of very low to moderate credibility of evidence.

Annex 6: Extracted data from 48 publications in 8 eligible systematic reviews with meta-analyses

Table A6.1: Study design

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Brehm (2003) RCT, parallel US **Funding:** ADA, U.S Public Health Service Grant; Cincinnati Children's Hospital Medical Center Clinical Research Center.	To compare effects of high MUFA and HCDs on body weight and glycaemic control in men and women with T2D. **Study duration**: 12 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** BMI 27 to 40 kg/m^2, age 30 to 75 y, stable body weight for preceding 6m, T2D diagnosis for at least 6 m, HbA1c, 6.5 to 9.0%, and treatment by diet or oral agents only (no insulin). **Exclusion criteria:** Pregnancy/lactation; active cardiac, pulmonary, renal, liver, or gastrointestinal disease; untreated thyroid disease or hypertension; triacylglycerol >500 mg/dl, use of medications that may alter lipid metabolism, corticosteroids, and weight loss drugs. **Study power:** NR
Brinkworth (2004) RCT, parallel Australia **Funding:** Meadow Lea Foods, Mascot, NSW, Australia.	Long-term weight loss and health outcomes at 1 y follow-up, after a 12-week intensive intervention consisting of two low-fat, weight-loss diets with differing protein content. **Study duration:** 16 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol HDL, LDL, total cholesterol:HDL ratio **[PP]**	**Inclusion criteria:** Not specified. Recruited (via public advertisement) 66 overweight/obese adults (BMI: 27 to 40 kg/m^2) with T2D who completed health-screening questionnaire. **Exclusion criteria:** Proteinuria or a history of liver, unstable cardiovascular, respiratory, or gastrointestinal disease or a malignancy. **Study power:** NR [Retrospective calculation: 87 and 52 individuals respectively required in each group to detect significant difference in weight regain of 4.5 kg (5% body weight) between groups with 88% power, p=0.05.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Brunerova (2007) RCT, parallel Czech Republic **Funding:** VZ MSM 0021620814	To compare influence of a hypocaloric, high-fat diet enriched with MUFA and conventional diet on weight loss and metabolic parameters in obese non-diabetic and obese T2D adults. **Study duration:** 3 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, HDL **[NR]**	**Inclusion criteria: O**bese non-diabetic or T2D adults (a (i) FBG ≥7 mmol/l or random blood glucose ≥11.1 mmol/l on 2 occasions or, if on only 1 occasion, then with symptoms (polyuria, polydipsia, etc.), or blood glucose at 120 min of an oral glucose tolerance test (OGTT) ≥11.1 mmol/l; (ii) fasting C-peptide >800 pmol/l, (iii) negative for anti-GAD and anti IA2, and (iv) being treated with diet or with oral glucose-lowering drugs**.** **Exclusion criteria:** Presence of pancreatic, biliary or thyroid diseases. **Study power:** Estimated 13/group would provide >80% to detect difference in FBG of 0.8mmol/L between 0 and 3 months. Estimated 13/group would be needed to have 90% power to detect 0.8% mean decrease in HbA1c.
Daly (2006) RCT, parallel UK **Funding:** Diabetes UK	To examine effects of a 3 m programme of dietary advice to restrict CHO intake compared with reduced-portion, low-fat advice in obese adults with poorly controlled T2D. **Study duration**: 3 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL **[PP]**	**Inclusion criteria:** Obese (BMI ≥30 kg/m^2) adults with poorly controlled T2D (HbA1c, 8 to 12%) with a serum creatinine <150 µmol/l. **Exclusion criteria:** Patients with unexplained weight loss or ketosis. **Study power:** 37/group [To detect 1% difference in HbA1c achieved between the 2 interventions with 80% CI. SD for change in HbA1c from feasibility studies informed power calculation.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Davis (2009) RCT, parallel US **Funding:** Robert C. Atkins Foundation and Diabetes Research and Training Center (P60 DK020541) and by Clinical and Translational Science Award UL1 RR025750.	To compare effects of a 1 y intervention with a low CHO and a low-fat diet on weight loss and glycaemic control in adults with T2D. **Study duration**: 12 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults aged >18 y with T2D diagnosis for at least 6 m, BMI ≥25 kg/m^2, and HbA1c, 6 to 11%. **Exclusion criteria:** Weight change of >10 lbs within 3m of screening, kidney disease, active liver or gallbladder disease, CHD, history of severe (requiring hospitalisation) hypoglycaemia, or use of weight loss medications. **Study power:** 105 [80% power to detect mean (SD) difference in weight of 2 (3) kg and HbA1c of 0.7 (1.3) % between dietary arms.]
De Bont (1981) RCT, parallel UK **Funding:** NR	To investigate the effect of LFD advice on dietary response in insulin independent diabetic Women **Study duration:** 6 **Outcomes**: Weight, HbA1c, triacylglycerols, total cholesterol, HDL **[PP]**	**Inclusion criteria:** Diabetic women, aged 35 to 64 y and free of other diseases **Exclusion criteria:** NR **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Dyson (2007) RCT, parallel UK **Funding:** Medisense UK, Abbott Laboratories.	To assess impact of LCD on body weight, HbA1c, ketone and lipid levels in diabetic and non-diabetic adults. **Study duration**: 3 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Age >18 y, BMI >25 kg/m^2, without T2D or with T2D treated by diet alone or metformin monotherapy. **Exclusion criteria:** T1D or T2D individuals treated by insulin, sulphonylurea or thiazolidinedione, pregnant or breastfeeding women or women without adequate contraception, major psychiatric disease, including eating disorders, history of alcohol or drug abuse, serum creatinine >150 µmol/l, abnormal liver function tests, or any known malignancy. **Study power:** 10/group [9/group would give >90% power, p=0.05]
Elhayany (2010) RCT, parallel Israel **Funding:** NR	To compare effects of a low CHO Mediterranean, a traditional Mediterranean, and the 2003 ADA diet on health parameters. **Study duration**: 12 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** (i) age 30 to 65 y; (ii) T2D diagnosed within 1 to 10 y; (iii) BMI 27 to 34 kg/m^2; (iv) last HbA1c measurement 7 to 10%; (v) last plasma triacylglycerol, 1.8 to 4.5 mmol/l; (vi) last serum creatinine <123.2 µmol/l; and (vii) no change in diabetes medication for at least 3 m before entering study. **Exclusion criteria:** (i) proliferative diabetic retinopathy; (ii) current insulin treatment; (iii) active oncologic or psychiatric disease; and (iv) uncontrolled hypothyroidism or hyperthyroidism. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Esposito (2009) RCT, parallel Italy **Funding:** Second University of Naples	To compare effects of a low-CHO Mediterranean-style or a LFD on need for anti-hyperglycaemic drug therapy in adults with newly diagnosed T2D. **Study duration**: 48 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL **[ITT]**	**Inclusion criteria:** Age 30 to 75 y, BMI>25 kg/m^2, (HbA1c <11%, sedentary (<1 h of physical activity/wk) with no participation in weight-reduction programs and with stable weight (±2 kg) in past 6 m. **Exclusion criteria:** Pregnancy/breastfeeding, use of any investigational drug in previous 3 m, use of agents affecting glycaemic control, any condition that might compromise adherence to diet regimens. **Study power:** 87/group [Assuming 80% power, 87/group required to observe HbA1c difference of 0.25%. To allow for 25% dropout rate, assigned 215 patients.]
Fabricatore (2011) RCT, parallel US **Funding:** National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Research Resources.	To compare effects of lifestyle modification programmes that prescribe low-GL vs. LFDs. **Study duration:** 9 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Age 18 to 65 y, diagnosis of T2D, BMI of 27 to 45 kg/m^2 (maximum weight, 136 kg). **Exclusion criteria:** T1D, uncontrolled hypertension (>160/100 mm Hg), thyroid disease, unstable angina, malignant arrhythmias, myocardial infarction in past year, cancer (active or in remission <5 y), clinically significant psychosocial impairment, or any history of cerebrovascular, renal, hepatic, or protein-wasting diseases. Pregnant or lactating women. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Facchini (2003) RCT, parallel US **Funding**: NR	To evaluate whether a CHO-restricted, low-iron available, polyphenol-enriched (CR-LIPE) diet may delay and improve the outcome of diabetic nephropathy to a greater extent than standard protein restriction. **Study duration**: 47 (22) **Outcomes**: NR **[NR]**	**Inclusion criteria:** T2D patients referred to nephrology clinics for various degrees of renal failure (GFR 15 ÷ 75 ml/min) and otherwise unexplained proteinuria (350 ÷ 12,000 mg/day), no history of offending drug or toxin exposure, inactive sediment on urinalysis and symmetrical kidneys of normal or increased size on abdominal ultrasonography. **Exclusion criteria:** NR **Study power**: 93/group [Sample size calculation was estimated on the basis of former survival analysis from CHO-restricted animal experiments and from iron depletion experiments leading to 50% reduction of insulin resistance.]
Garg (1994) RCT, cross-over US **Funding**: Pfizer Inc, New York, National Institutes of Health grants, the Medical Research Service of the San Diego Veterans Affairs Medical Center.	To study effects of variation in CHO content of diet on glycaemia and plasma lipoproteins in patients with non-insulin-dependent diabetes (NIDDM). **Study duration**: 3.5 **Outcomes**: NR **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power**: NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Goday (2006) RCT, parallel Spain **Funding**: Pronokal Group	To evaluate short-term safety and tolerability of a VLCK diet (≤50 g of CHO daily) in an interventional weight loss program including lifestyle and behavioural modification support (Diaprokal Method) in adults with T2D **Study duration:** 4 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT & PP]**	**Inclusion criteria:** age, 30 to 65 y, previous diagnosis of T2D and BMI between30 and 35 kg/m^2. **Exclusion criteria:** T2D duration > 10 y, insulin therapy, HbA1c ≥9% and fasting C-peptide <1 ng/ml, impaired renal function (GFR <60 ml/min per 1.73 m^2), impaired liver function, alcohol intake ≥40 g/day for men and ≥24 g/day for women, pregnancy, lactation, or severe eating or psychiatric disorder. **Study power:** 45/group [Sample size of 38 per group was estimated necessary to validate hypothesis that the occurrence of an α error would be equivalent in the 2 study groups, with an α error of 0.05 and a statistical power of 80%. Dropout rate of 15% anticipated in both groups; therefore, aimed to recruit 45 per group].
Goldstein (2011) RCT, parallel Israel **Funding:** None	To compare an Atkins-like diet to a conventional ADA-recommended diet. **Study duration**: 12 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL **[ITT]**	**Inclusion criteria:** Aged 35 to 75 y, BMI 30 to 9.9 kg/m^2, HbA1c >7%, not receiving insulin, microalbumin excretion <60 mg/day. **Exclusion criteria:** Serum creatinine level >1.4 mg/dl, DBP >100 mmHg or SBP >180 mmHg, liver disease, LDLc >160 mg/dl, use of psychiatric medications, osteoporosis, cancer, food allergies, consumption of LCD in past 6 m. **Study power:** 20/group [>80% power to detect between group differences in loss of 3kg or more in body weight and reduction of ≥1% in HbA1c. 56 adults recruited to allow for expected drop-outs.]

First author (year) **study design, location, funding**	**Objectives, study duration (months),** **outcomes, type of analysis** (PP/ITT)]	**Inclusion and exclusion criteria, study power**
Guldbrand (2012) RCT, parallel Sweden **Funding:** University Hospital of Linköping, Linköping University, County Council of Östergötland, and Diabetes Research Centre of Linköping University.	To compare effects of a 2-year intervention with a LFD or a LCD based on four group-meetings to achieve compliance. **Study duration**: 24 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** T2D diagnosis, treated with diet with or without additional oral anti-diabetic medication, incretin-based therapy or insulin. **Exclusion criteria:** Difficulties in understanding Swedish, severe mental disease, malignant disease or abusing drugs. **Study power:** 30/group [Power of study not reported; size of study based on earlier 6 m pilot study (n=28) randomised to same diet.]
Hockaday (1978) RCT, parallel UK **Funding:** British Diabetic Association and International Sugar Research Foundation Inc.	To determine the effect of LCD and the HCD, modified-fat diet on circulating metabolites and on diabetic complications. **Study duration**: 12 **Outcomes**: Weight, FBG, triacylglycerols, total cholesterol **[ITT]**	**Inclusion criteria:** Newly diagnosed T2D adults not requiring either insulin or oral hypoglycaemic agents; aged 65 years or under. **Exclusion criteria:** suffering from co-existent major illness; endocrine disease, myocardial infarction, neurological deficit following cerebrovascular accident or liver disease. **Study power**: NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Iqbal (2009) RCT, parallel US **Funding:** VA Merit Review Entry program	To determine whether comparable results to those of short-term, intensive interventions comparing a LCD versus LFD in obese, diabetic adults could be achieved over 24 m using a low-intensity intervention that approximates what is feasible in outpatient practice. **Study duration:** 24 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults with T2D (defined as a pre-existing clinical diagnosis or by use of insulin or oral antidiabetic medications), age ≥18 y, BMI ≥30 kg/m^2. **Exclusion criteria:** Serum creatinine >1.5 mg/ dl (133 µmol/l), urine albumin to creatinine ratio >200 µg/ mg, HbA1c <6.0% or >12.0%, hypoglycaemic or hyperglycaemic episodes in past month requiring assistance, weight loss ≥5% in past 3 m, participation in weight-loss program, or use of weight-loss medications. **Study power:** 50/group [80% power to detect 5 +/-12% greater weight loss in the LCD group. Anticipated drop-out rate of 35% target - enrolment set at n= 156.]
Jenkins (2014) RCT, parallel Canada **Funding:** Canola Council of Canada, Agriculture and Agri-Food Canada, and Loblaw Companies Canada.	To determine the combined effect of alpha-linolenic acid (ALA), MUFA, and low GL on glycaemic control and CVD risk factors in T2D. **Study duration:** 3 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[ITT]**	**Inclusion criteria:** At least a 6 m history of T2D, taking a stable dose of oral antihyperglycaemic agents for at least previous 2 m, and HbA1c between 6.5% (48 mmol/mol) and 8.5% (69 mmol/mol) at initial screening and at visit 1 wk before randomisation. **Exclusion criteria:** HbA1c <6.5% or >8.5%; not on diabetes medication **Study power:** 140 participants [on basis of data from a 12-wk study in T2D (16) from an ANCOVA model, would require 116 participants to detect a treatment difference in HbA1c change of 0.15% with SD of 0.48% [assuming a=0.05, 1 2 b=0.8,using r=0.8 to account for the high degree of correlation between successive measure.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Jonasson (2014) RCT, parallel Sweden **Funding:** NR	To investigate effects of diet on inflammation in T2D by comparing a traditional LFD with a LCD. **Study duration:** 6 **Outcomes**: BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Diagnosis of T2D treated with diet with or without oral glucose-lowering medication or insulin. **Exclusion criteria:** Difficulties in understanding the Swedish language, severe mental disease, malignant disease or drug abuse. **Study power:** 30/group [Based on an earlier 6 m pilot study of 28 participants, no. of participants was increased to at least 30/group.]
Jonsson (2009) RCT, cross-over Sweden **Funding**: Crafoordska stiftelsen, Region Skåne and Lund University	To compare effects of a Paleolithic ('Old Stone Age') diet and a diabetes diet as generally recommended on risk factors for CVD in T2D adults not treated with insulin. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerol, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** adults with T2D and C-peptide > 0, unaltered medical T2D treatment and stable weight since 3 m before study start, HbA1c >5.5%, creatinine< 130 µmol/L, liver enzymes <4 times their respective upper reference value, no chronic oral or injection steroid treatment, no acute coronary event or change in β-blockers or thyroxin medication 6 m before study start . **Exclusion criteria**: change in β-blocker or thyroxin medication, chronic oral or injection steroid treatment, warfarin treatment, creatinine > 130 µmol/L or liver enzymes > 4 times their respective upper reference value, acute coronary event, and physical or psychological illness. **Study power**: 15 participants [pre-study power calculation showed that 15 participants would be required to detect, with 80% power and at a significance level of 5%, a 15% reduction in AUC glucose 0 to 120.]

First author (year) **study design, location, funding**	**Objectives, study duration (months),** **outcomes, type of analysis** (PP/ITT)]	**Inclusion and exclusion criteria, study power**
Krebs (2012) RCT, parallel New Zealand **Funding:** Health Research Council of New Zealand (06/337)	To compare effectiveness of low-fat high-protein and low-fat high-CHO dietary advice on weight loss, using group-based interventions, among overweight adults with T2D. **Study duration:** 24 **Outcomes**: Weight, HbA1c, FBG, triacylglycerol, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Established T2D (WHO criteria), aged 30 to 76 y, BMI ≥27 kg/m^2. **Exclusion criteria:** On weight-reducing medications, weight loss of >5% in past 3 m, psychiatric or eating disorder, HbA1c >9.5% (80 mmol/mol) or renal disease (estimated GFR <60 ml/min or urine albumin:creatinine ratio >30 mg/mmol), abnormal liver enzymes, heart failure, active malignancy or MI in preceding 6 m. **Study power:** 420 participants [required to detect clinically important differences between groups of 1.9% in weight, 2 cm in waist circumference (80% power, p=0.05).]
Larsen (2011) RCT, parallel Australia **Funding:** Meat and Livestock Australia (MLA)	To determine whether HPDs are superior to HCDs for improving glycaemic control in individuals with T2D. **Study duration:** 12 **Outcomes**: Weight, HbA1c, triacylglycerol, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Adults with T2D; aged 30 to 75 y; BMI, 27 to 40 kg/m^2; HbA1c, 6.5 to 10%. **Exclusion criteria:** Significant heart disease, stroke in previous 3 m, renal disease (proteinuria or serum creatinine >0.13 mmol/l), liver disease, or malignancy. **Study power:** 46/group [80% power (at 2-sided 5% level) to detect a difference of 0.5% in HbA1c between groups assuming SD of 0.85%.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Luger (2013) RCT, parallel Austria **Funding:** NR	To determine feasibility and efficacy of a HPD vs standard diet for weight maintenance in T2D adults on insulin requirement, body weight and metabolic parameters. **Study duration**: 3 **Outcomes:** Weight, BMI, HbA1c, FBG, triacylglycerols, HDL, LDL, total cholesterol:HDL ratio **[PP]**	**Inclusion criteria:** T2D adults on insulin therapy. **Exclusion criteria:** MI within last 6 m, stroke, impaired renal function (creatinine >1.3 mg dl – 1), parameters of liver function 2-times higher than normal and intake of protein-rich food supplements. **Study power:** NR
Mayer (2014) RCT, parallel US **Funding:** NIH T32 grant: ST32DK007012-35. Funding for original study: Department of Veterans Affairs.	To determine glycaemic, weight, and pertinent adverse effects of two weight-loss diet plans in T2D adults and to compare the intensity of anti-glycaemic agent use. **Study duration**: 11 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[NR]**	**Inclusion criteria:** Adults with T2D, aged ≤70 y and BMI 27 to 30 kg/m^2 plus an obesity-related disease, or BMI 30 kg/m^2. **Exclusion criteria:** Adults with T1D, unstable chronic disease, or disease that would interfere with participation; serum creatinine >1.5 mg/dl in men and >1.3 mg/dl in women; HbA1c >11%. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
McLaughlin (2007) RCT, parallel US **Funding:** National Institutes of Health Grants	To determine whether weight loss or metabolic improvement differed as a function of macronutrient composition (prescribed diets moderately restricted in either CHO or fat). **Study duration:** 4 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** BMI 27 to 36 kg/m^2, FPG concentration 7.2 to 8.3 mmol/l, no use of anti-hyperglycaemic medications, and stable weight for 3 m. Adults on anti-hypertensive or cholesterol-lowering drugs or aspirin allowed to continue their medications. **Exclusion criteria:** NR **Study power:** NR
Nielsen (2005) CT (non-randomised), parallel Sweden **Funding:** Medical research committee, Blekinge, Sweden	To observe FBG, long-term glycaemic control, body weight and BMI in obese T2D adults on LCD with a control group on HCD. **Study duration:** 6 **Outcomes**: Weight, HbA1c, FBG **[ITT]**	**Inclusion criteria:** FBG >6 mmol/L, HbA1c >5.6%, use of glucose-lowering medication. **Exclusion criteria:** NR **Study power:** NR
Parker (2002) RCT, parallel Australia **Funding:** Meadow Lea Foods	To determine effect of a high-protein weight loss diet compared with lower-protein diet on fat and lean tissue and fasting and postprandial glucose and insulin concentrations. **Study duration:** 3 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Pedersen (2014) RCT, parallel Australia **Funding:** NR	To determine if a high protein to CHO ratio in an energy reduced diet is beneficial for metabolic control and CVD risk factors without negatively affecting renal function. **Study duration**: 12 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Overweight or obese (BMI 27 kg/m^2) adults with T2D, aged 18 to 75 y, with albuminuria (30 to 600 mg/24 h or an albumin to creatinine ratio of 3.0 to 60.0 mg/mmol, estimated GFR >40 ml/min/1.73 m^2). **Exclusion criteria:** Impaired kidney function not due to diabetes. **Study power:** NR
Pohl (2005) RCT, parallel Germany **Funding:** Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany	To investigate effects of long-term treatment with a new enteral formula low in CHOs and high in MUFAs, in comparison with a standard formula, on glycaemic control in tube-fed T2D patients. **Study duration**: 3 **Outcomes**: HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT & PP]**	**Inclusion criteria:** Age ≥40 y, insulin-treated T2D with HbA1c ≥7.0% and/or FBG concentrations 46.66 mmol/l, indication for tube feeding due to dysphagia caused by neurological disorders. **Exclusion criteria:** T1D, known allergy against ingredients of study diets, intake of other enteral or oral nutrition, parenteral nutrition, significant renal, hepatic or heart disease, and systemic glucocorticoid therapy within 2 weeks before and/or after study admission. **Study power**: 184 [Sample size of 184 calculated to give 90% power to detect medium sized (relevant) group difference.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Pohl (2009) RCT, parallel Germany **Funding**: NR	Stage I (Pohl et al 2005) of a pre-planned 2-stage study provided good evidence for improved glycaemic control with a disease specific enteral formula low in CHOs and high in MUFAs, fish oil, chromium and antioxidants in insulin-treated T2D. The study was continued with stage II to confirm these beneficial effects. **Study duration**: 3 **Outcomes**: HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** Patients aged ≥40 y with insulin-treated T2D with HbA1c ≥7.0% and/or FBG (FG) >6.7 mmol/L (>120 mg/dL) and indication for long-term tube feeding due to dysphagia caused by neurological disorders (eg, stroke, traumatic brain injury, hypoxic brain damage). **Exclusion criteria:** T1D, known allergy against ingredients of investigational products, intake of other enteral diets, parenteral nutrition, severe liver disease, renal failure, congestive heart failure, human immunodeficiency virus and systemic glucocorticoid therapy within the last 2 weeks before and/or after study admission. **Study power**: NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Rock (2014) RCT, parallel US **Funding:** School of Medicine, UCSD	To test whether a weight loss programme promotes greater weight loss, glycaemic control, and improved CVD risk factors compared with control conditions and whether there is a differential response to higher versus lower CHO intake. **Study duration:** 12 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP and ITT]**	**Inclusion criteria:** T2D confirmed by physician; aged ≥18 y; BMI 25 to 45 kg/m^2; not pregnant/ breastfeeding or planning pregnancy; no eating disorders, food allergies, or food intolerances; no history of bariatric surgery; able to perform step test for assessing cardiopulmonary fitness. **Exclusion criteria:** Weight loss >10 lb in past 3 m; history or presence of a psychiatric disorder or any condition that would interfere with participation. HbA1c >11% (97 mmol/mol), fasting triacylglycerol >600 mg/dL, serum creatinine ≥1.4 mg/dL (women) or 1.5 mg/dL (men). **Study power:** 75/group [90% power for primary aim with dropout rate of up to 20%; also 90% power to detect between group HbA1c differences of 0.5% (6 mmol/mol).]
Samaha (2003) RCT, parallel US **Funding:** Veterans Affairs Healthcare Network Competitive Pilot Project Grant	To test whether severely obese adults with high prevalence of T2D or metabolic syndrome would have greater weight loss, without detrimental effects on risk factors for atherosclerosis, while on a CHO-restricted diet than on a calorie and fat-restricted diet. **Study duration:** 6 **Outcomes**: Weight, HbA1c, FBG **[ITT]**	**Inclusion criteria:** Age ≥18 y and BMI ≥35 kg/m^2. **Exclusion criteria:** Serum creatinine >1.5 mg/dl (132.6 µmol/L); hepatic disease; severe, life-limiting medical illness; inability of diabetic subjects to monitor own glucose levels; active participation in a dietary programme; use of weight loss medications. **Study power:** 50/group [80% power to demonstrate a mean (+/-) weight loss 5±12 kg greater in low CHO than in low fat group.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Saslow (2014) RCT, parallel US **Funding:** William K. Bowes, Jr. Foundation and the Mount Zion Health Fund	Compare effects of two diets on HbA1c and other health-related outcomes in overweight/obese adults with T2D or prediabetes **Study duration:** 3 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, HDL, LDL **[ITT]**	**Inclusion criteria:** Aged ≥18 y with T2D diagnosis (HbA1c ≥6.5) or prediabetes (HbA1c >6.0. BMI ≥25 kg/m$^{2)}$. **Exclusion criteria:** non-English speaking, substance abuse, mental health or medical condition making it difficult to take part, use of oral glucocorticoids or weight loss medications; pregnant or planning pregnancy, breastfeeding or <6 m postpartum; history of or planned weight loss surgery; vegan; using insulin or taking >3 oral hypoglycaemic medications. **Study power:** NR
Sato (2017) RCT, parallel Japan **Funding:** Mishima Kaiun Memorial Foundation	To compare effectiveness and safety of LCD with calorie restricted diet. **Study duration:** 6 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, HDL, LDL **[PP]**	**Inclusion criteria:** age >20 to <75 y, 2) HbA1c >7.5% for more than 3 m, BMI >23 kg/m2, had received at least two educational programs on calorie restricted diets. **Exclusion criteria:** Diagnosis of retinopathy, severe neuropathy, serious kidney disease (serum creatinine >2.0 mg/dL and/or with microalbuminuria), serious liver disease excluding fatty liver, acute heart failure within 3 m, active malignancy, serious pancreatic disease, pregnancy, serious infectious disease, trauma injury, alcohol dependency. **Study power:** 33/group [Estimated difference in HbA1c reduction between 2 groups of 0.4% power of 90%.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Shai (2008) RCT, parallel Israel **Funding:** Nuclear Research Center Negev, Atkins Research Foundation, S Daniel Abraham International Center for Health and Nutrition, Ben Gurion University.	To compare effectiveness and safety of 3 nutritional protocols: a low-fat, restricted-calorie diet; a Mediterranean, restricted-calorie diet; and a low-CHO, non-restricted calorie diet. **Study duration:** 24 **Outcomes**: NR **[ITT]**	**Inclusion criteria:** Age 40 to 65 y, BMI ≥27 kg/m^2 or presence of T2D (according to ADA criteria) or CHD, regardless of age and BMI. **Exclusion criteria:** Pregnant or lactating, serum creatinine ≥2 mg/dl (177 µmol/L), liver dysfunction, gastrointestinal problems, cancer, or participating in another diet trial. **Study power:** 100/group [Type I error of 5%, >90% power to detect significant differences in weight loss.]
Shirai (2013) RCT, parallel Japan **Funding:** Weight Control Association	To clarify usefulness of a 24-wk formula diet once a day in combination with conventional low-caloric diet in obese adults with T2D. **Study duration:** 6 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, HDL, LDL **[PP]**	**Inclusion criteria:** T2D adults (HbA1c ≥6.0%): BMI >25 kg/m^2. **Exclusion criteria:** Massive proteinurea; malignancy; history of hepatitis, cardiovascular events, respiratory or gastrointestinal diseases; uncontrolled hypertension; pregnant or breast feeding. **Study power:** NR
Stern (2004) RCT, parallel US **Funding:** Veterans Affairs Healthcare Network Competitive Pilot Project Grant	To compare a LCD versus low-fat weight loss diet in severely obese adults with a high prevalence of diabetes or metabolic syndrome. **Study duration**: 12 **Outcomes**: HbA1c, FBG **[ITT & PP]**	**Inclusion criteria:** Aged ≥18 y, BMI ≥35 kg/m^2. **Exclusion criteria:** Serum creatinine >133 µmol/L (>1.5 mg/dL), hepatic disease, severe life-limiting medical illness, inability to self-monitor glucose levels, active use of a weight loss programme or weight loss medication. **Study power:** 50/group [80% power to detect a 5kg greater mean weight loss in low CHO group.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Strychar (2009) RCT, parallel Canada **Funding:** Canadian Institutes of Health Research, Institute of Nutrition and Metabolism.	To compare effects of a eucaloric diet higher in CHO/lower in fat vs diet lower in CHO/higher in MUFA on post-meal triacylglycerol concentrations and other CVD risk factors in non-obese T1D adults with good glycaemic control. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[ITT]**	**Inclusion criteria:** Adults with T1D on intensive insulin therapy. **Exclusion criteria:** BMI ≥30 kg/m^2, HbA1c ≥8.4% and major diabetes complications. **Study power:** NR
Tay (2014) RCT, parallel Australia **Funding:** National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.	To compare the effects of a very low-CHO, high unsaturated / low saturated fat diet with those of a high unrefined CHO, low-fat diet (HC) on glycaemic control and CVD risk factors in T2D. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** Overweight/obese adults (BMI 26 to 45 kg/m^2, age 35 to 68 y) with T2D (previously diagnosed with HbA1c ≥7.0% [53 mmol/mol] and/or taking antiglycaemic medication). **Exclusion criteria:** T1D; proteinuria; impaired renal function (eGFR ,60 mL/min); abnormal liver function (alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase ≥2.5 times normal upper limit); any significant endocrinopathy history of malignancy; liver, respiratory, gastrointestinal, or CVD; pregnancy/lactation; clinical depression; history of/or current eating disorder; smoking. **Study power:** NR [The trial was designed to have 80% power to detect 0.7% (7.7 mmol/mol) absolute difference in HbA1c between diets.]

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Tay (2015) RCT, parallel Australia **Funding:** National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.	To compare effects of a very-low-CHO, high unsaturated fat, low saturated fat (LC) diet with a high CHO, low-fat (HC) diet on glycaemic control and CVD risk factors in T2D after 52 wks. **Study duration**: 12 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** As above (Tay, 2014) **Exclusion criteria:** As above (Tay, 2014) **Study power:** As above (Tay, 2014)
Tay (2018) RCT, parallel Australia **Funding:** National Health and Medical Research Council of Australia; Agency for Science, Technology and Research, Singapore.	To examine whether a low-CHO, high-unsaturated/low-saturated fat diet improves glycaemic control and CVD risk factors in overweight and obese adults with T2D. **Study duration**: 24 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** As above (Tay, 2014) **Exclusion criteria:** As above (Tay, 2014) **Study power:** As above (Tay, 2014)
Walker (1995) RCT, cross-over Australia **Funding:** Diabetes Australia; food products supplied by Olive Oil Council and Meadow Lea Foods Australia	To examine effects of a high-CHO low-fat (HCLF) and a modified-fat diet on body weight and metabolic control in adults with T2D. **Study duration**: 3 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power:** NR

First author (year) **study design, location, funding**	**Objectives, study duration (months),** **outcomes, type of analysis** (PP/ITT)]	**Inclusion and exclusion criteria, study power**
Walker (1999) RCT, cross-over Australia **Funding:** The National Health and Medical Research Council of Australia	To compare effects of a high CHO and a monounsaturated fat diet (high-MUFA) on body fat distribution and sex hormones in post-menopausal women with T2D. **Study duration**: 6 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** NR **Study power:** NR
Watson (2016) RCT, parallel Australia **Funding:** Pork Cooperative Research Centre; study foods donated by various companies.	To compare effects of a HPD to an isocaloric higher-CHO diet on cardiometabolic risk factors for 12 weeks in energy restriction (~30% reduction) followed by 12 weeks of energy balance whilst performing regular exercise. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[ITT]**	**Inclusion criteria:** T2D, aged 18 to 70 y, HbA1c 6.5 to 10.5%, BMI >25 kg/m^2, weight ≤135 kg, non-smoker (>6 m), proficient in written and spoken English, age-appropriate cognitive abilities. **Exclusion criteria:** Liver, kidney, GI or CVD, respiratory disease (apart from asthma), retinopathy, malignancy (within last 6 m), proteinuria, uncontrolled hypertension (>170/100), taking medication for a neurological or psychiatric condition, neurological or psychiatric condition, history of head/brain injury, musculoskeletal injury or peripheral vascular disease sufficient to impede exercise, undertaking a weight loss programme or taking appetite suppressants, pregnant or lactating. **Study power:** NR

First author (year) study design, location, funding	Objectives, study duration (months), outcomes, type of analysis (PP/ITT)]	Inclusion and exclusion criteria, study power
Westman (2008) RCT, parallel US **Funding:** Robert C Atkins Foundation	To test whether a diet lower in CHO would lead to greater improvement in glycaemic control over 24 weeks in obese adults with T2D. **Study duration**: 6 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerol, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[PP]**	**Inclusion criteria:** T2D >1 y (HbA1c >6.0%), onset of diabetes after age 15 y, no history of diabetic ketoacidosis, age 18 to 65 y, BMI 27 to 50 kg/m^2, desire to lose weight. **Exclusion criteria:** Unstable or serious medical condition; significant co-morbid illnesses such as liver disease, kidney disease (serum creatinine >1.5 mg/dL), cancer; pregnancy; nursing mothers. **Study power:** 60 participants [80% power in a completers analysis to detect a clinically meaningful change in HbA1c (absolute change of 1.0%, SD=1.5).]
Wolever (2008) RCT, parallel Canada **Funding:** Canadian Institutes of Health Research; foods donated by various companies.	To compare effects of altering the GI or amount of CHO on HbA1c, plasma glucose, lipids, and C-reactive protein in adults with T2D. **Study duration**: 12 **Outcomes**: Weight, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL, total cholesterol:HDL ratio **[Unclear]**	**Inclusion criteria:** Men/non-pregnant women with T2D (FPG ≥7.0 mmol/L or plasma glucose ≥11.1 mmol/L 2 h after 75-g OGTT) managed by diet alone. **Exclusion criteria:** Use of insulin, any hypoglycaemic or anti-hyperglycaemic medication, stroke, MI, major surgery within previous 6 m, serum triacylglycerol >10 mmol/L, any major debilitating condition or drug likely to alter nutrient absorption, use of oral steroids, substance or alcohol abuse, allergy/intolerance to >1 of study key foods. **Study power:** 42/group [80% probability and a 2-tailed $p<0.05$ to allow detection of difference of 0.36% in rate of change of HbA1c between low CHO and low GI diets.]

First author (year) **study design, location, funding**	**Objectives, study duration (months),** **outcomes, type of analysis** (PP/ITT)]	**Inclusion and exclusion criteria, study power**
Wycherley (2010) RCT, parallel Australia **Funding:** National Heart Foundation of Australia; Diabetes Australia Research Trust; Pork Cooperative Research Centre; Geroge Weston Foods.	To evaluate effects of 2 low-fat hypocaloric diets differing in the CHO-to-protein ratio, with and without resistance exercise training on weight loss, body composition and CVD risk outcomes in overweight/obese adults with T2D. **Study duration**: 4 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, total cholesterol, HDL, LDL **[PP]**	**Inclusion criteria:** NR **Exclusion criteria:** Proteinuria; a malignancy; history of liver, kidney, CVD, respiratory, or gastrointestinal disease; uncontrolled hypertension; pregnant or lactating; smoker; using insulin, any musculoskeletal injury or joint or peripheral vascular disease sufficient to impede exercise or had participated in regular physical exercise in 6 m prior to study. **Study power:** NR
Yamada (2014) RCT, parallel Japan **Funding:** NR	To examine effects of a non-calorie-restricted, LCD in Japanese adulst unable to adhere to a calorie-restricted diet. **Study duration:** 6 **Outcomes**: Weight, BMI, HbA1c, FBG, triacylglycerols, HDL, LDL **[ITT]**	**Inclusion criteria:** Individuals with T2D, with HbA1c 6.9 to 8.4%, who had received guidance regarding calorie restriction at least once. **Exclusion criteria:** Proteinuria >1.0 g/day, serum creatinine >132 µmol/L (men) or 106 µmol/L (women), aspartate aminotransferase or alanine aminotransferase >3 times upper limit of normal, history of MI or stroke within 6 m before study entry or an absolute change in the HbA1c of >1.0% within 6 m before study entry. **Study power:** 22 [90% power, α=0.05 to detect change in HBA1c over 6 m of 0.0±0.5% in calorie restricted group and 0.7±0.5% in LCD group]

Table A6.2: Description of intervention and participant characteristics

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Brehm (2003)	[1] High MUFA	62 (43)	19 (31)	NR	NR	HbA1c 6.5 to 9%; diagnosis of T2D for at least 6 m
	[2] High CHO	62 (52)	10 (16)	NR		
	[All]	124 (95)	29 (23)	56.5 (0.8)*		
Brinkworth (2004)	[1] High protein	33(19)	14(42)	60.9 (1.8)*	NR	NR
	[2] Low protein	31 (19)	12(39)	62.7 (1.8)*		
	[All]	64 (38)	26 (41)	NR		
Brunerova (2007)	[1] Hypocaloric, high-fat enriched with MUFA	14	0 (0)	54.7 (3.8)	NR	FBG >7 mmol/l or random blood glucose >11.1 mmol/l on ≥ 2 occasions OR blood glucose at 120 min of OGTT >11.1 mmol/l
	[2] Conventional	13	0 (0)	51.2 (3.3)		
	[All]	27	0 (0)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age, years (SD or SEM*)	T2D duration (years)	Inclusion criteria for T2D diagnosis
Daly (2006)	[1] Low CHO	51 (40)	11 (22)	58.2 (1.6)*	NR	HbA1c 8 to 12%
	[2] Low fat	51 (39)	12 (24)	59.1 (1.5)*		
	[All]	102 (79)	23 (23)	NR		
Davis (2009)	[1] Low CHO	55 (47)	8 (15)	54 (6)	NR	HbA1c 6 to 11%; diagnosis of T2D for at least 6 m
	[2] Low fat	50 (44)	6 (12)	53 (7)		
	[All]	105 (91)	14 (13)	NR		
De Bont (1981)	[1] Low CHO	NR (65)	NR	54 (8)	6.9	NR
	[2] Low fat	NR (71)	NR	56 (7)	6.9	
	[All]	148 (136)	12 (8)	NR	NR	

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Dyson (2007)	[1] Low CHO	6 (0)	0 (0)	NR	NR	NR
	[2] Diabetes UK nutritional recommendations	7 (6)	1 (14)	NR		
	[All]	13 (12)	1 (8)	54 (9)		
Elhayany (2010)	[1] Low CHO Mediterranean	85 (61)	24 (28)	55.5 (6.5)	5.5 (3.8)	Last HbA1c measurement 7 to 10%
	[2] Traditional Mediterranean	89 (63)	26 (29)	57.4 (6.1)	6.2 (9.9)	
	[3] ADA 2003	85 (55)	30 (35)	56.0 (6.1)	5.1 (2.6)	
	[All]	259 (179)	80 (31)	55	NR	
Esposito (2009)	[1] Low CHO Mediterranean	108 (98)	10 (9)	52.4 (11.2)	Newly diagnosed	ADA criteria; HbA1c <11%
	[2] Low fat	107 (97)	10 (9)	51.9 (10.7)		
	[All]	215 (195)	20 (9)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age, years (SD or SEM*)	T2D duration (years)	Inclusion criteria for T2D diagnosis
Fabricatore (2011)	[1] Low GL	40 (24)	16 (40)	52.8 (1.4)*	NR	NR
	[2] Low fat	39 (26)	13 (33)	52.5 (1.3)*		
	[All]	79 (50)	29 (37)	NR		
Facchini (2003)	[1] CHO-restricted	100 (91)	9 (9)	59 (10)	9 (4)	NR
	[2] Standard protein restriction	91 (79)	12 (13)	60 (12)	10 (5)	
	[All]	191 (170)	21 (11)	NR	NR	
Garg (1994)	[1] High MUFA	NR	NR	NR	NR	NR
	[2] High CHO	NR	NR	NR		
	[All]	42 (21)	1 (2)	54 (9)		
Goday (2006)	[1] VLCKD	45 (40)	5 (11)	54.89 (8.81)	NR	NR
	[2] Low calorie diet	44 (36)	8 (18)	54.17 (7.97)		
	[All]	89 (76)	23 (15)	54.53 (8.37)		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age, years (SD or SEM*)	T2D duration (years)	Inclusion criteria for T2D diagnosis
Goldstein (2011)	[1] Modified Atkins diet	26 (14)	12 (46)	57 (9)	7.7 (4.9)	HbA1c >7%
	[2] ADA 2001 calorie-restricted diet	26 (16)	10 (38)	55 (8)	8.2 (5.8)	
	[All]	52 (30)	22 (42)	NR	NR	
Guldbrand (2012)	[1] Low CHO	30 (26)	4 (13)	61.2 (9.5)	9.8 (5.5)	NR
	[2] Low fat	31 (28)	3 (10)	62.7 (11)	8.8 (6.2)	
	[All]	61 (54)	7 (11)	NR	NR	
Hockaday (1978)	[1] Low CHO	54 (54)	NR	53	Newly diagnosed	NR
	[2] High CHO, modified fat	39 (39)	NR	50		
	[All]	93 (93)	NR	NR		

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Iqbal (2009)	[1] Low CHO	70 (28)	42 (60)	60.0 (8.9)	NR	Pre-existing clinical diagnosis or use of insulin or oral anti-diabetic medications. Excluded if HbA1c <6% or >12%
	[2] Low fat	74 (40)	34 (46)	60.0 (9.5)		
	[All]	144 (68)	76 (53)	59.4 (9.2)		
Jenkins (2014)	[1] Wholegrain diet	70 (55)	15 (21)	59 (10)	7.6 (6.9)	HbA1c 6.5 to 8.5%
	[2] Low GL with ALA and MUFA	71 (64)	7 (10)	59 (10)	7.5 (5.4)	
	[All]	141 (119)	22 (16)	NR	NR	
Jonasson (2014)	[1] Low CHO	30 (30)	0 (0)	61 (9.5)	9.8 (5.5)	NR
	[2] Low fat	31 (31)	0 (0)	63 (11)	8.8 (6.2)	
	[All]	61 (61)	0 (0)	NR	NR	

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age, years (SD or SEM*)	T2D duration (years)	Inclusion criteria for T2D diagnosis
Jonsson (2009)	[1] Paleolithic diet	NR	NR	66 (6)	6	HbA1c >5.5%
	[2] EAD recommendations	NR	NR	63 (6)	11	
	[All]	26 (26)	0 (0)	64 (6)	NR	
Krebs (2012)	[1] Low fat higher protein	207 (144)	63 (30)	57.7 (9.9)	8.3 (6.6)	WHO criteria
	[2] Low fat higher CHO	212 (150)	62 (29)	58.0 (9.2)	8.2 (6.3)	
	[All]	419 (294)	125 (30)	57.9 (9.5)	NR	
Larsen (2011)	[1] High protein	53 (43)	15 (28)	59.6 (57.5, 61.8) [range]	8.7 (6.8, 10.5)	HbA1c 6.5 to 10%
	[2] High CHO	46 (37)	10 (22)	58.8 (55.8, 61.7) [range]	8.6 (6.6, 10.6)	
	[All]	99 (80)	25 (25)	NR	NR	
Luger (2013)	[1] High-protein	22 (20)	2 (9)	61.0 (5.7)	17.6 (9.4)	NR
	[2] EAD recommendations	22 (22)	0 (0)	63.7 (5.2)	16.2 (9.2)	
	[All]	44 (42)	2 (5)	62.4 (5.6)	NR	

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Mayer (2014)	[1] Low CHO	22	0 (0)	56.6 (7.3)	5.9 (4.4)	NR
	[2] Low fat + orlistat	24	0 (0)	54.7 (8.4)	7.3 (8.9)	
	[All]	46	0 (0)	NR	NR	
McLaughlin (2007)	[1] 40% CHO	14 (14)	0 (0)	57 (7)	NR	FPG 7.2 to 8.3 mmol/l
	[2] 60% CHO	15 (15)	0 (0)	56 (7)		
	[All]	29 (29)	0 (0)	NR		
Nielsen (2005)	[1] Low CHO	16 (16)	0 (0)	57.1 (6.2)	13 (5.5)	HBA1c >5.6% and FBG >6 mmol/l
	[2] High CHO	15 (15)	0 (0)	58.6 (10.1)	8.5 (5.4)	
	[All]	31 (31)	0 (0)	NR	NR	

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Parker (2002)	[1] High protein	33 (28)	5 (15)	Male, 63.4 (1.7)*; female, 58.7 (2.2)*	NR	NR
	[2] Lower protein	31 (26)	5 (16)	Male, 64.2 (3.8)*; female, 60.9 (2.3)*		
	[All]	64 (54)	10 (16)	NR		
Pedersen (2014)	[1] High protein to CHO ratio	38 (21)	17 (45)	59.4 (2.2)*	12.4 (2.5)	NR
	[2] Standard protein diet	38 (24)	14 (37)	62.4 (1.7)*	7.9 (1.0)	
	[All]	76 (45)	31 (41)	NR	NR	
Pohl (2005)	[1] Low CHO, high MUFA	39 (21)	18 (46)	71 (42, 86)	NR	HbA1c ≥7% and/or FBG >6.66mmol/l
	[2] Standard formula	39 (23)	16 (41)	72.0 (51, 87)		
	[All]	78 (44)	34 (44)	NR		

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Pohl (2009)	[1] Low CHO, high MUFA	52 (34)	18 (35)	74	NR	
	[2] Standard formula	52 (21)	31 (60)	69		
	[All]	104 (55)	49 (47)	NR		
Rock (2014)	[1] Lower CHO	77 (67)	10 (13)	57.3 (8.6)	NR	T2D diagnosis confirmed by physician
	[2] Lower fat	74 (69)	5 (7)	55.5 (9.2)		
	[3] Usual care	76 (68)	8 (11)	56.8 (9.3)		
	[All]	227 (204)	23 (10)	NR		
Samaha (2003)	[1] Low CHO	26 (17)	9 (35)	53 (9)	NR	NR
	[2] Low fat	26 (12)	14 (54)	54 (9)		
	[All]	52 (29) (includes participants without T2D)	23 (44)	NR		

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age, years (SD or SEM*)	T2D duration (years)	Inclusion criteria for T2D diagnosis
Saslow (2014)	[1] Very low CHO ketogenic	16 (15)	1 (6)	64.8 (7.7)	7.8 (7.5)	HbA1c ≥6.5%
	[2] Moderate CHO, calorie restricted, low fat	18 (17)	1 (6)	55.1 (13.5)	6.4 (4.9)	
	[All]	34 (32)	2 (6)	NR	NR	
Sato (2017)	[1] Low CHO	33 (30)	1 (3)	60.5 (10.5)	14.0 (7.8 to 18.5) [median (IQR)]	HbA1c >7.5% for >3 m
	[2] Calorie restricted	33 (32)	3 (9)	58.4 (10.0)	13.0 (9.0 to 20.0) [median (IQR)]	
	[All]	66 (62)	4 (6)	NR	NR	
Shai (2008)	[1] Low CHO, non-restricted calorie	19 (12)	7 (37)	52 (7)	NR	ADA criteria
	[2] Mediterranean, restricted calorie	15 (13)	2 (13)	53 (6)		
	[3] Low fat, restricted calorie	12 (11)	1 (8)	51 (7)		
	[All]	46 (36)	10 (22)	52 (7)		

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Shirai (2013)	[1] Formula (high protein, low CHO, low fat)	120 (119)	1 (1)	50.5 (11.8)	NR	HbA1c ≥6.0%
	[2] Conventional	120 (110)	10 (8)	51.7 (10.9)		
	[All]	240 (229)	11 (5)	NR		
Stern (2004)	[1] Low CHO	27 (18)	9 (33)	53 (9)	NR	FBG >6.94 mmol/L or use of antidiabetic medications
	[2] Conventional	27 (16)	11 (41)	54 (9)		
	[All]	54 (34)	20 (37)	NR		
Strychar (2009)	[1] Low CHO, high MUFA	(15)	Unclear	NR	Participants with T1D	Adults with T1D on intensive insulin therapy; HbA1c >8.4% excluded
	[2] High CHO, low fat	(15)	Unclear	NR		
	[All]	(30) not clear how many recruited	Unclear	37.9 (8.1)		

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Tay (2014)	[1] Low CHO, high unsaturated fats, low saturated fat	58 (46)	12 (21)	58 (7)	NR	HbA1c ≥7.0% or taking anti-glycaemic medication
	[2] High CHO, low-fat	57 (47)	10 (18)	58 (7)		
	[All]	115 (93)	22 (19)	58 (7)		
Tay (2015)	[1] Low CHO, high unsaturated fats, low saturated fat	58 (41)	17 (29)	58 (7)	7 (5) [SD]	HbA1c ≥7.0% or taking diabetes medication
	[2] High CHO, low-fat	57 (37)	20 (35)	58 (7)	9 (7) [SD]	
	[All]	115 (78)	37 (32)	58 (7)	NR	
Tay (2018)	[1] Low CHO, high unsaturated fats, low saturated fat	58 (33)	25 (43)	58 (7)	6 (4 to 7) [CI]	HbA1c ≥7.0% or taking diabetes medication
	[2] High CHO, low-fat	57 (28)	29 (51)	58 (7)	8 (6 to 10) [CI]	
	[All]	115 (61)	54 (47)	58 (7)	NR	

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Walker (1995)	[1] Modified fat [2] High CHO, low fat [All]	NR NR NR (48)	NR NR NR	NR NR 58.3 (2.1)	NR	NR
Walker (1999)	[1] High MUFA [2] High CHO [All]	NR NA 34 (21)	NR NA 13 (38)	NR NR 58 (7)	3 (3) 3 (3) NR	NR
Watson (2016)	[1] High protein [2] High CHO [All]	32 (23) 29 (21) 61 (44)	9 (28) 8 (28) 17 (28)	54 (8) 55 (8) 55 (8)	7.9 (6.0) [SD] 6.5 (4.2) [SD] NR	HbA1c 6.5 to 10.5%

Author (year)	Intervention groups	Number of participants at baseline (completers)	Loss to follow-up, n (%)	Mean age, years (SD or SEM*)	T2D duration (years)	Inclusion criteria for T2D diagnosis
Westman (2008)	[1] Low CHO, ketogenic	38 (21)	17 (45)	51.8 (7.3)	NR	Diagnosis >1 y (confirmed by HbA1c >6.0%); onset of T2DM after 15 y of age
	[2] Low GI, reduced calorie	46 (29)	17 (37)	51.8 (7.8)		
	[All]	84 (50)	34 (40)	NR		
Wolever (2008)	[1] Low CHO, high MUFA	54 (44)	10 (19)	58.6 (1.2)*	NR	FPG ≥7.0 mmol/L or ≥11.1 mmol/L 2 h after 75g OGTT on ≥1 occasion within 2 m of randomisation
	[2] Low GI, high CHO	56 (45)	11 (20)	60.6 (1.0)*		
	[3] High GI, high CHO	52 (41)	11 (21)	60.4 (1.1)*		
	[All]	162 (130)	32 (20)	NR		
Wycherley (2010)	[1] High protein	21 (12)	9 (43)	NR	NR	NR
	[2] Energy-restricted standard CHO	19 (16)	3 (16)	NR		
	[All]	40 (28)	12 (30)	55.0 (8.4)		

Author (year)	**Intervention groups**	**Number of participants at baseline (completers)**	**Loss to follow-up, n (%)**	**Mean age, years** (SD or SEM*)	**T2D duration** (years)	**Inclusion criteria for T2D diagnosis**
Yamada (2014)	[1] Low CHO	12 (12)	0 (0)	63.3 (13.5)	8.9 (3.6) [SD]	HbA1c level 6.9 to 8.4%
	[2] Conventional calorie-restricted	12 (12)	0 (0)	63.2 (10.2)	9.5 (4.8) [SD]	
	[All]	24 (24)	0 (0)	63.3 (11.7)	NR	

Table A6.3: Macronutrient intakes, dietary approach and physical activity recommendations

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Brehm (2003)		**Prescribed intakes**						
	[1] High MUFA	NR	45	15	40 [MUFA: 20]	NR	NR	NR
	[2] High CHO	NR	60	15	25	NR	NR	NR
		Reported intakes						
	[1] High MUFA	1550	46	16	38 [MUFA: 14%]	NR	NR	NR
	[2] High CHO	1550	54	16	28 [MUFA: 9%]	NR	NR	NR
	Food-based dietary advice: Meal plan based on calorie allotment: 1) food groups with healthy foods, serving sizes, number of servings allowed in each group, 2) list of "free" minimal calorie foods, 3) sample menu. Meal plans included following food groups: starches, fruits, vegetables, low-fat dairy products, meat/meat substitutes, fat. Compared with high CHO, high MUFA included fewer servings of starches, fruit, and meat/meat substitutes and more servings of fat (emphasising olive and canola oils); also included an additional food group of beans, legumes, nuts. **Intervention approach/intensity:** 1:1 sessions/group sessions/meal plans. Weekly in first 2 months, bi-weekly in months 3 and 4, monthly in months 5 to 12 for either individual or group counselling session (alternating every other visit). **Assessment of dietary adherence:** 3-day food diary during weeks of scheduled sessions. Dietitians rated participants' adherence on scale of 1 to 10 (1/did not follow diet; 10/followed diet all the time); participants estimated own adherence on scale of 1 to 10. Average adherence ratings calculated for each participant. There were no significant differences in adherence ratings between diet groups or between dietitian and participant ratings. **Physical activity:** Participants instructed to maintain their level of physical activity; if not physically active, then advised to walk 30 minutes/day several days/wk. Participants wore pedometers and recorded pedometer readings and physical activity. Analysis of pedometer readings showed no differences between diet groups or over time.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Brinkworth (2004)		**Prescribed intakes**						
	[1] Low protein	1601.3	55	15	30 [SFA: 8, PUFA: 5, MUFA: 12]	NR	NR	NR
	[2] High protein	NR	40	30	30 [SFA: 8, PUFA: 5, MUFA: 12]	NR	NR	NR
		Reported intakes						
	[1] Low protein	NR	NR	NR	NR	NR	NR	NR
	[2] High protein	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: 30 g/day fibre prescribed to both groups. For first 12 wks, diets prescriptive fixed menu plans and participants supplied with key foods (60% TE) including pre-weighed portions of beef and chicken for 6 meals/week, biscuits, low-fat cheese (3% fat), diet yogurt, skim milk powder for group 1, rice for group 2. Other differences between diets: amount of meat and chicken (200 vs 100 g), fruit (200 vs 300 g) and wholemeal bread (3 vs 4 slices). Alcohol not permitted. List of free choice vegetables and salad was provided. **Intervention approach/intensity:** 1:1 sessions with dietician/every 2 weeks for 12 weeks; for succeeding 52 weeks contact between participants and diet counsellors minimal. **Assessment of dietary adherence:** NR **Physical activity:** No specific guidelines provided.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Brunerova (2007)		**Prescribed intakes**						
	[1] Hypocaloric, high-fat diet enriched with MUFA	NR	45	10	45 [SFA: 11.25, PUFA: 11.25, MUFA: 22.5]	NR	NR	NR
	[2] Conventional diet	NR	60	10	30 [SFA: 10, PUFA: 10, MUFA: 10]	NR	NR	NR
		Reported intakes						
	[1] Hypocaloric, high-fat diet enriched with MUFA	NR	NR	NR	NR	NR	NR	NR
	[2] Conventional diet	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: 20 grams per day of fibre prescribed to both intervention groups. **Intervention approach/intensity:** 1:1 sessions with dietitian and provided with written information about their diet and instructed to follow prescribed menus for 1st 2 weeks/every 2 wks. **Assessment of dietary adherence:** Food diary (number of days not specified). **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Daly (2006)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	≤70	NR	NR
	[2] Low fat	NR	NR	NR	NR	NR	NR	To reduce fat intake and portion size
		Reported intakes						
	[1] Low CHO	1290 (70.6) [SEM]	33.5 (1.55) [SEM]	26.4 (0.96) [SEM]	40.1 (1.60) [SFA:13.9 (0.71)] [SEM]	109.5 (6.44) [SEM]	NR	NR
	[2] Low fat	1434 (78.6) [SEM]	45.2 (1.31) [SEM]	20.9 (0.58) [SEM]	32.9 (1.07) [SFA:11.0 (0.47)] [SEM]	168.6 (10.84) [SEM]	NR	NR
	Food-based dietary advice: To address some concerns of low CHO diet, emphasis also placed on incorporating at least ½ pint milk and 1 piece fruit into daily CHO allowance to improve vitamin/mineral intake. Healthy eating group given standard healthy eating advice, focusing on reducing fat intake reducing portion sizes. **Intervention approach/intensity:** 1 individual consultation, 3-monthly group sessions and final assessment consultation. Dietary advice standardises by using written and predetermined educational materials. Two 1:1 sessions and 2 group sessions. **Assessment of dietary adherence:** 5-day food diary (completed at week 11). **Physical activity:** Advice on importance, and ideas for increasing physical activity, incorporated into the 3 education sessions for both interventions (further details not provided).							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Davis (2009)		**Prescribed intakes**						
	[1] Low CHO	NR	5 to 6 (increase by 5 g/wk)	NR	NR	20 to 25 (increase by 5 g/wk)	NR	NR
	[2] Low fat	NR	NR	NR	25	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1642 (600) [SD]	33.4 (13.2) [SD]	22.7 (6.7) [SD]	43.9 (10.8) [SFA 28.7 (9.6), PUFA 17.4 (8.0), MUFA 40.7 (10.4)] [SD]	NR	NR	NR
	[2] Low fat	1810 (590) [SD]	50.1 (10.0) [SD]	18.9 (4.7) [SD]	30.8 (10.2) [SFA 30.2 (5.4), PUFA 21.4 (8.6), MUFA 38.1 (6.9)] [SD]	NR	NR	NR
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/1st month individual study visits 1-2 times/week then every 6 weeks; measured weight and BP and received counselling on diabetes management, adjustment of diabetes medication and dietary adherence. Nutrition counselling by dietitian: 45 minutes at randomisation and over 12 months, 6 visits (30 minutes). **Assessment of dietary adherence:** 24-h recall by interview at baseline, 6 and 12 months. Participants were also instructed to keep daily food diaries, which were reviewed during the study visits. **Physical activity:** Recommendations to achieve 150 minutes each week but stated that physical activity not emphasis of study. Note that they did not have objective measures of physical activity but given similarity of findings in both groups at 1 year, unlikely that there were significant changes in physical activity in either group.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
De Bont (1981)		**Prescribed intakes**						
	[1] Low CHO	NR	40	NR	NR	NR	NR	NR
	[2] Low fat	NR	NR	NR	30	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1340	38	19.9	41.8 [SFA 19.9, PUFA 4.8, MUFA 16.6]	NR	NR	NR
	[2] Low fat	1197	45.7	22.7	31.1 [SFA 12, PUFA 7.8, MUFA 11.3]	NR	NR	NR
	Food-based dietary advice: Group 1: NR. Group 2: reducing dairy products and fat from meat, and substituting margarines in order to improve the saturated:polyunsaturated fat balance. **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Dyson (2007)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	40	NR	NR
	[2] Diabetes UK nutritional recommendations	NR	NR	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1313 (205) [SD]	17.3 (9.7) [SD]	31.1 (6.9) [SD]	46.2 (10.6) [SD]	56.8 (26.5) [SD]	97.2 (18.9) [SD]	69.3 (25.6) [SD]
	[2] Diabetes UK nutritional recommendations	1593 (277) [SD]	39.3 (12.8) [SD]	19.8 (3.1) [SD]	34.4 (7.8) [SD]	167.3 (60.4) [SD]	79.5 (16.6) [SD]	62.7 (22.4) [SD]
	Food-based dietary advice: Advised to take ≥200 mL milk/day and 4 to 5 portions fruit and vegetables/day especially low CHO vegetables (for example, salads, green leafy vegetables). Low CHO group advised to include lean meats, poultry, fish, game, low-fat dairy products, avoid large amounts of saturated fat and use MUFA. Healthy eating group advised to reduce total and saturated fat, eat 5 portions fruit and vegetables daily and adopt diet with low GI. **Intervention approach/intensity:** 1:1 session/every month. **Assessment of dietary adherence:** 3-day food diary. **Physical activity:** All encouraged to increase physical activity and exercise at moderate intensity for 30 minutes at least 5 and preferably 7 days/week.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Elhayany (2010)		**Prescribed intakes**						
	[1] Low CHO Mediterranean	NR	35	20	45 [SFA, 7%; PUFA, 15%; MUFA, 23% of total fat]	NR	NR	NR
	[2] Traditional Mediterranean	NR	50	20	30 [SFA, 7%; PUFA, 12%; MUFA, 10% of total fat]	NR	NR	NR
	[3] American Diabetes Association 2003	NR	50	20	30 [SFA, 7%; PUFA, 12%; MUFA, 10 % of total fat]	NR	NR	NR
		Reported intakes						
	[1] Low CHO Mediterranean	2221.6 (1086.6) [SD]	41.9	NR	[PUFA: 12.9, MUFA: 14.6]	NR	NR	NR
	[2] Traditional Mediterranean	2221.6 (1086.6) [SD]	45.2	NR	[PUFA: 11.5, MUFA: 12.8]	NR	NR	NR
	[3] American Diabetes Association 2003	2221.6 (1086.6) [SD]	45.4	NR	[PUFA: 11.2, MUFA: 12.6]	NR	NR	NR
	Food-based dietary advice: Diet groups 1 and 2 included only low GI CHO; Group 3 diet included mixed GI CHO. **Intervention approach/intensity**: 1:1 sessions every 2 weeks for 1 year/24 times. **Assessment of dietary adherence:** 24 h recall, FFQ. Evaluated results of the FFQ administered at 6 months. FFQs showed a good adherence to the assigned diet and participants followed up every 2 weeks in primary care clinic. **Physical activity:** All advised to engage in 30 to 45 minutes of aerobic activity at least 3 days/week.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Esposito (2009)		**Prescribed intakes**						
	[1] Low CHO Mediterranean	1500 for women 1800 for men	≤50	NR	≥30	NR	NR	NR
	[2] Low fat	1500 for women 1800 for men	NR	NR	≤30 [SFA: ≤10]	NR	NR	NR
		Reported intakes						
	[1] Low CHO Mediterranean	1895	44.2	18.0	[SFA:10]	NR	NR	NR
	[2] Low fat	1895	51.8	17.9	[SFA:9.4]	NR	NR	NR
	Food-based dietary advice: Group 1 diet rich in vegetables and wholegrains and low in red meat (replaced with poultry and fish). Group 2 diet rich in wholegrains and restricted additional fats, sweets and high-fat snacks. **Intervention approach/intensity:** 1:1 sessions/monthly in 1st year and bi-monthly thereafter. **Assessment of dietary adherence:** Food diary (does not specify how many days). Assessed adherence to the diets by session attendance and review of the diaries. **Physical activity:** All received guidance on increasing level of physical activity: at least 30 minutes/day walking, swimming or aerobic ball games. With gradual progression toward a goal of 175 minutes of moderate-intensity physical activity/week. Participants in both groups increased time being physically active (from 45 [SD, 12] to 125 min/wk [SD, 41] in Group 1 and from 43 [SD, 13] to 119 min/wk [SD, 48] in Group 2). Not significant between-group difference in amount of increase.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Fabricatore (2011)		**Prescribed intakes**						
	[1] Low fat	1200.8 to 1501 (BW 113.4 kg); 1501 to 1801 (BW >113.4 kg)	NR	NR	≤30	NR	NR	40 to 50 in 1200.8 to 1501; 50 to 60 in 1501 to 1801
	[2] Low GL	1200.8 to 1501 (BW 113.4 kg); 1501 to 1801 (BW >113.4 kg)	NR	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Low fat	1676	49.8	18.9	32.9	NR	NR	NR
	[2] Low GL	1575.9	41.3	20.4	39.8	NR	NR	NR
	Food-based dietary advice: Group 1 encouraged to model diet on a 'low-fat pyramid'; Group 2 given 'low-GL Pyramid' and instructed to consume ≤3 and ≤1 serving/day of moderate GL and high GL items, respectively. **Intervention approach/intensity:** Group (n=4 to 8) sessions/weekly for 20 weeks and bi-weekly for additional 20 weeks. **Assessment of dietary adherence:** 3-day food diary (2 weekdays and 1 weekend day). **Physical activity:** At least 50 minutes/ week of moderate-intensity activity (eg, brisk walking) and to increase to at least 175 minutes/week over first 20 weeks of treatment.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Facchini (2003)		**Prescribed intakes**						
	[1] CHO-restricted	NR	35	25 to 30	30	NR	NR	NR
	[2] Standard protein restriction	NR	65	10	25	NR	NR	NR
		Reported intakes						
	[1] CHO-restricted	NR	NR	NR	NR	NR	NR	NR
	[2] Standard protein restriction	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: Group 1: substitution of iron-enriched red meats (beef and pork) with iron-poor white meats (poultry and fish) and with protein-enriched food items known to inhibit iron absorption, eg, dairy, eggs, and soy; elimination of all beverages other than tea, water, and red wine. Milk recommended for breakfast. Tea was highly recommended. Red wine was not to exceed 150 mL with lunch and 150 mL with dinner. Outside mealtimes, water was the only approved beverage; exclusive use of polyphenol-enriched extra-virgin olive oil for both dressing and frying. Group 2: Avoid sucrose-containing beverages. **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Garg (1994)		**Prescribed intakes**						
	[1] High MUFA	NR	40	15	45 [SFA: 10, PUFA: 10, MUFA: 25]	NR	NR	NR
	[2] High CHO	NR	55	15	30 [SFA: 10, PUFA: 10, MUFA: 10]	NR	NR	NR
		Reported intakes						
	[1] High MUFA	NR	NR	NR	NR	NR	NR	NR
	[2] High CHO	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: Group 1: olive oil was used a main source of fat when preparing food in metabolic kitchen. Group 2: NR **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Goday (2006)		**Prescribed intakes**						
	[1] Very low calorie-ketogenic diet	NR	NR	NR	NR	<50	0.8 to 1.2 g/ideal BW	NR
	[2] Low calorie diet	NR	45 to 60	10 to 20	<30	NR	NR	NR
		Reported intakes						
	[1] Very low calorie-ketogenic diet	NR	NR	NR	NR	NR	NR	NR
	[2] Low calorie diet	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: Group 1: participants advised to consume fat rich in MUFA and protein from poultry and fish rather than from saturated fat-rich red meat. Group 2: NR **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Unclear.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Goldstein (2011)		**Prescribed intakes**						
	[1] Modified Atkins diet	NR	NR	NR	NR	25 to 40	NR	NR
	[2] American Diabetes Association (2001) calorie-restricted diet	NR	NR	10 to 20	[SFA 9 to 10; PUFA 8 to 10; MUFA 18 to 20]	NR	NR	NR
		Reported intakes						
	[1] Modified Atkins diet	1725 (600) [SD]	19.7	NR	NR	85 (35) [SD]	102 (37) [SD]	111 (45) [SFA 32 (17), MUFA 29 (15)] [SD]
	[2] American Diabetes Association (2001) calorie-restricted diet	1937 (376) [SD]	43	NR	NR	208 (61) [SD]	90 (12) [SD]	85 (24) [SFA 24 (8), MUFA 23 (10)] [SD]
	Food-based dietary advice: Group 1: advised to consume fat rich in MUFA and protein from poultry and fish rather than from saturated fat-rich red meat. Group 2: NR **Intervention approach/intensity:** 1:1 sessions/weekly counselling for first 12 weeks, thereafter monthly meetings (25 times). **Assessment of dietary adherence:** 3-day food diary. Participants requested to rate themselves each week on scale of 1 to 10 on adherence to the diet; then measured monthly until end of 1-year follow-up. In parallel, ketogenic effect of a low CHO diet in the Atkins group was evident in 61% of participants at 6 weeks, but only in 18%, 20% and 7% of participants at 3, 6 and 12 months, respectively, indicating low adherence to CHO restriction target. **Physical activity:** All advised to engage in physical aerobic activities (walking, swimming, running on treadmill) 3 times/week for at least 30 m throughout trial. Data on physical activity collected through questionnaire. Both groups similarly increased their reported exercise activity during trial by 1 hour/week.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Guldbrand (2012)		**Prescribed intakes**						
	[1] Low CHO	1800 kcal for men, 1600 kcal for women	20	30	50	NR	NR	NR
	[2] Low fat	1800 for men, 1600 for women	55 to 60	10 to 15	30 [SFA: <10]	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1251 [SD]	31 (6) [SD]	24 (4) [SD]	44 (5) [SFA 19 (2), PUFA 6 (2), MUFA 16 (3)] [SD]	NR	NR	63 (24) [SD]
	[2] Low fat	1459 [SD]	47 (7) [SD]	20 (2) [SD]	31(7) [SFA 13 (3), PUFA 5 (2), MUFA 11 (3)] [SD]	NR	NR	52 (22) [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** Group sessions/4 times. **Assessment of dietary adherence:** 3-day food diary (2 weekdays and 1 weekend day). During first 6 months adherence to proposed diet was comparatively good in both groups as judged by mean values of macronutrient intake. **Physical activity:** No information given to change level of activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Hockaday (1978)		**Prescribed intakes**						
	[1] Low CHO	1500	40	20	40 [SFA 28, PUFA 12]	150	75	67 [SFA 46, PUFA 21]
	[2] High CHO, modified fat	1500	54	20	26 [SFA 10, PUFA 16]	203	75	43 [SFA16, PUFA 27]
		Reported intakes						
	[1] Low CHO	NR	NR	NR	NR	NR	NR	NR
	[2] High CHO, modified fat	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: Patients were encouraged to eliminate simple sugars as far as possible, but special attention was not given to dietary fibre, thus various complex CHO foods predominated. **Intervention approach/intensity**: 1:1 sessions, dietitian repeated dietary advice; appointments after 1 m and then 3-monthly intervals. **Assessment of dietary adherence:** NR **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Iqbal (2009)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	30	NR	NR
	[2] Low fat	NR	NR	NR	<30	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1609.9	47.9	16.9	34.2	NR	NR	NR
	[2] Low fat	1573.5	46.7	17.6	33.6	NR	NR	NR
	Food-based dietary advice: Group 1: encouraged to select wholegrain products and foods with high fibre content, to consume healthy fats (eg, MUFA and PUFA) and to minimise intake of saturated and trans fats. Group 2: encouraged to increase fruit and vegetable intake. **Intervention approach/intensity:** Group sessions and opportunity to meet with the dietitian individually/2 hours weekly for the first month, thereafter every 4 weeks. **Assessment of dietary adherence**: 24-hour recall. **Physical activity:** All encouraged to engage in at least 30 minutes of moderate activity at least 5 times/week. No differences between groups in amount of self-reported physical activity at any time point.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Jenkins (2014)		**Prescribed intakes**						
	[1] Wholegrain diet	NR	NR	NR	NR	NR	NR	NR
	[2] Low GL with α-linolenic acid and MUFA	NR	NR	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Wholegrain diet	1539	38.5	19.8	37.2 [SFA: 7.6, PUFA: 9.4, MUFA: 17.4]	NR	NR	NR
	[2] Low GL with α-linolenic acid and MUFA	1630	49.2	19.8	27.4 [SFA: 7.9, PUFA: 6.8, MUFA: 9.9]	NR	NR	NR
	Food-based dietary advice: Dietary advice on the low GL with α-linolenic diet emphasised low GI foods, including legumes, barley, pasta, parboiled rice and temperate-climate fruit. For the wholegrain diet, participants instructed to avoid white-flour products and replace with wholewheat breakfast cereals, study breads, brown rice. **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Maintain the usual level of physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Jonasson (2014)		**Prescribed intakes**						
	[1] Low fat	1600 for women and 1800 for men	55 to 60	NR	30	NR	NR	NR
	[2] Low CHO	1600 for women and 1800 for men	20	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Low fat	1553 (427) [SD]	49 (5.9) [SD]	20 (3.5) [SD]	29 (5.4) [SFA 11 (2.1), PUFA 5.1 (1.9), MUFA 11 (2.5)] [SD]	182 (51) [SD]	NR	53 (24) [SD]
	[2] Low CHO	1384 (366) [SD]	25 (8.4) [SD]	23 (3.7) [SD]	49 (7.5) [SFA 20 (3.7), PUFA 7.7 (2.4), MUFA 18 (3.2)] [SD]	82 (28) [SD]	NR	79 (25) [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** Group sessions/4 times. **Assessment of dietary adherence:** 3-day food diary. Adherence to proposed diet was similar in both groups. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Jonsson (2009)		**Prescribed intakes**						
	[1] Paleolithic diet	NR	NR	NR	NR	NR	NR	NR
	[2] European Association for Diabetes recommendations	NR	NR	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Paleolithic diet	1581 (295) [SD]	32 (7) [SD]	24 (3) [SD]	39 (5) [SD]	NR	NR	NR
	[2] The European Association for Diabetes recommendations	1878 (379) [SD]	42 (7) [SD]	34 (6) [SD]	20 (4) [SD]	NR	NR	NR
	Food-based dietary advice: Diabetes diet: evenly distributed meals with increased intake of vegetables, root vegetables, dietary fibre, wholegrain bread and other wholegrain cereal products, fruits and berries; decreased intakes of total fat with more unsaturated fat. Majority of dietary energy should come from CHOs from foods naturally rich in CHO and dietary fibre. Concepts of GI and varied meals through meal planning by Plate Model were explained. Salt intake <6 g/day. Paleolithic diet: lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts; excluding dairy products, cereal grains, beans, refined fats, sugar, candy, soft drinks, beer and addition of salt. Following recommended in limited amounts: eggs (≤2/day), nuts, dried fruit, potatoes (≤1/day), rapeseed or olive oil (≤1 tablespoon/day), wine (≤1 glass/day). Intakes of other foods not restricted. No advice regarding proportions of food categories (eg, animal vs plant foods). **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Same advice to all participants.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Krebs (2012)		**Prescribed intakes**						
	[1] Low fat high protein	NR	40	30	30	NR	NR	NR
	[2] Low fat high CHO	NR	55	15	30	NR	NR	NR
		Reported intakes						
	[1] Low fat high protein	1713.7 (471.7) [SD]	45.5 (6.9) [SD]	20.6 (3.9) [SD]	32.8 (6.3) [SFA 12.5 (3.2)] [SD]	194.1 (56.6) [SD]	87 (23.5) [SD]	63.7 (24.3) [SFA 24.4 (10.4)] [SD]
	[2] Low fat high CHO	1695.3 (442.5) [SD]	48.1 (6.6) [SD]	20.3 (4.4) [SD]	30.4 (6.8) [SFA 11.5 (3.6)] [SD]	203.4 (56.6) [SD]	84.4 (22.4) [SD]	58.9 (23.1) [SFA 22.4 (10.5)] [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** Group sessions/ every 2 weeks for first 6 months; every month for the second 6 months (1 hour). Weekly text or email reminders and motivational messages. **Assessment of dietary adherence:** 3-day food diary. Drop-out rate high in both groups, with 'difficulty adhering' to either diet cited by participants as a major factor. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Larsen (2011)		**Prescribed intakes**						
	[1] High protein	1529.6	40	30	30 [SFA 7, PUFA 10, MUFA 13]	NR	NR	NR
	[2] High CHO	1530	55	15	30 [SFA 7, PUFA 10, MUFA 13]	NR	NR	NR
		Reported intakes						
	[1] High protein	1592.7	41.8	26.5	30.7 [SFA 39.3% of total fat, PUFA 18.1 of total fat, MUFA 42.6 of total fat]	NR	NR	NR
	[2] High CHO	1584.1	48.2	18.9	32 [SFA 39.8 of total fat, PUFA 18.6 of total fat, MUFA 41.6 of total fat]	NR	NR	NR
	Food-based dietary advice: Group 1: encouraged to eat lean meat, chicken, fish. Groups 1 and 2: recommended CHO of low GI. **Intervention approach/intensity:** 1:1 sessions and group sessions/4 visits during the energy restrictive period and 5 visits during the 9 months of energy balance; group sessions every 3 months. **Assessment of dietary adherence:** 5-day food diary at baseline and 3-day food diary every 3 months during intervention period (1 day/month). In addition to self-reported dietary intakes, participants asked to rate their ability to self-manage their prescribed diet. After 12 m of following the prescribed diet, no significant difference between groups in median dietary self-management scores. **Physical activity:** Encouraged as a strategy to increase energy expenditure, in line with public health guidelines. Measured using validated Active Australia survey. No significant group difference in self-reported time spent in physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Luger (2013)		**Prescribed intakes**						
	[1] High protein	NR	40	30	30	NR	NR	NR
	[2] European Association for the Study of Diabetes	NR	55	15	30	NR	NR	NR
		Reported intakes						
	[1] High protein	1272.7 (337.8) [SD]	37.5 (6.6) [SD]	25.6 (4.7) [SD]	34.8 (6.1) [SD]	NR	NR	NR
	[2] European Association for the Study of Diabetes	1235.6 (325.4) [SD]	50.4 (7.6) [SD]	16.6 (3.2) [SD]	29.4 (5.0) [SD]	NR	NR	NR
	Food-based dietary advice/fibre/GI: Group 1: received data sheets referring to protein-rich foods. Major high protein sources included soy-based foods (eg, tofu), milk products, fish and poultry. Group 2: NR **Intervention approach/intensity**: 1:1 sessions/4 times. **Assessment of dietary adherence:** 24-hour recall (before enrolment) and 5-day food diary (for documentation of compliance). Based on the food records, participants showed good compliance with the prescribed diets. **Physical activity**: Instructed to maintain usual level of physical activity. Significant difference between the 2 groups: 28% of standard diet and 42% of high protein diet practiced sport or were physically active (p=0.045).							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Mayer (2014)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	≤20	NR	NR
	[2] Low fat and orlistat	NR	NR	NR	<30 [SFA <10]	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1707.9 (741.1) [SD]	17.8	NR	NR	75.9 (76.9) [SD]	NR	103.2 (58.1) [SD]
	[2] Low fat and orlistat	1419.6 (634.1) [SD]	43.9	NR	NR	155.8 (78.5) [SD]	NR	55.5 (41.7) [SD]
	Food-based dietary advice/fibre/GI: NR **Intervention approach/intensity:** NR **Assessment of dietary adherence:** 4-day food diary. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
McLaughlin (2007)		**Prescribed intakes**						
	[1] 40% CHO	NR	40	15	45 [SFA <7]	NR	NR	NR
	[2] 60% CHO	NR	60	15	25 [SFA <7]	NR	NR	NR
		Reported intakes						
	[1] 40% CHO	NR	43	19	38 [SFA 9]	NR	NR	NR
	[2] 60% CHO	NR	52	18	29 [SFA 8]	NR	NR	NR
	Food-based dietary advice: NR **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Required to maintain usual level of physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Nielsen (2005)		**Prescribed intakes**						
	[1] Low CHO	Men 1800; women 1600	20	30	50	<130	NR	NR
	[2] High CHO	Men 1600 to 1800; women 1400 to 1600	60	15	25	NR	NR	NR
		Reported intakes						
	[1] Low CHO	NR	NR	NR	NR	NR	NR	NR
	[2] High CHO	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice/fibre/GI: Group 1: recommended CHO consumption limited to vegetables and salad. Instead of bread, crisp/hard bread recommended, each containing 3.5 to 7 g of CHO. All processed CHOs (such as bread and pasta) and rice and potatoes excluded. Group 2: NR **Intervention approach/intensity:** Group sessions/NR. **Assessment of dietary adherence:** NR **Physical activity:** All instructed to exercise 30 minutes per day.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Parker (2002)		**Prescribed intakes**						
	[1] High protein	1600	40	30	25 [SFA 8, PUFA 5, MUFA 12]	130 to 230	NR	NR
	[2] Lower protein	1600	60	15	25 [SFA 8, PUFA 5, MUFA 12]	NR	NR	NR
		Reported intakes						
	[1] High protein	2029 (55) [SEM]	42.6 (0.4) [SEM]	27.7 (0.3) [SEM]	27.6 (0.3) [SFA 8.2 (0.2), PUFA 4.7 (0.1), MUFA 12.2 (0.2)] [SEM]	NR	NR	NR
	[2] Lower protein	1785 (74) [SEM]	55.0 (0) [SEM]	16.0 (0.3) [SEM]	26.7 (0.5) [SFA 7.6 (0.2), PUFA 4.8 (0.1), MUFA 11.6 (0.3)] [SEM]	NR	NR	NR
	Food-based dietary advice: Fixed menu plans; participants supplied with key foods (60% of TE), including: pre-weighed portions of beef and chicken suitable for 6 meals/week, biscuits, low-fat cheese (3% fat), diet yogurt, and skim milk powder for high protein diet and rice for low protein diet. Other differences between diets was in amount of meat and chicken (200 versus 100g), fruit (200 vs 300g), and wholemeal bread (3 vs 4 slices). Alcohol not permitted; list of free choice vegetables and salad was provided. **Intervention approach/intensity**: Participants supplied with key foods to assist with dietary compliance/group training provided on use of scales and keeping food records. **Assessment of dietary adherence:** 3-day food diary. Daily diet checklists assessed by dietitian at 2-wk intervals. **Physical activity:** Asked to maintain usual level of physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Pedersen (2014)		**Prescribed intakes**						
	[1] High protein to CHO ratio	1434	40	30	30 [SFA: 10]	130 to 230	90 to 120	NR
	[2] Standard protein diet	1434	50	20	30 [SFA: 10]	NR	55 to 70	NR
		Reported intakes						
	[1] High protein to CHO ratio	2004.8 (149.4) [SEM]	39.3	NR	NR	197.4 (16.3) [SEM]	130.6 (9.8) [SEM]	77.8 (6.6); SFA, 30.1 (2.7), PUFA, 12.3 (1.2); MUFA, 28.1 (2.4) [SEM]
	[2] Standard protein diet	1666.1 (87.7) [SEM]	45	NR	NR	187.6 (10.2) [SEM]	88.3 (4.0) [SEM]	63.3 (4.4); SFA, 22.9 (1.4); PUFA, 12.0 (1.2); MUFA, 22.3 (1.8) [SEM]
	Food-based dietary advice: NR **Intervention approach/intensity:** NR **Assessment of dietary adherence:** Compliance with protein prescription monitored by daily food checklist and FFQ (at baseline, 4m, 12 m) and by 24-hour urine urea excretion (UUE). No difference in UUE between groups at baseline. At 12 m, not significantly different from baseline, however adjusted UUE significantly different between groups (p=0.04) indicating compliance to protein prescription. **Physical activity:** All reported a moderate to low physical activity level and were asked to maintain this level throughout study.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Pohl (2005)		**Prescribed intakes**						
	[1] Low CHO high MUFA	NR	37	18	45 [MUFA 32]	NR	NR	NR
	[2] Standard formula	NR	52	18	30 [MUFA 17]	NR	NR	NR
		Reported intakes						
	[1] Low CHO high MUFA	NR	37	18	45 [MUFA 32]	NR	NR	NR
	[2] Standard formula	NR	52	18	30 [MUFA 17]	NR	NR	NR
	Food-based dietary advice: Not applicable **Intervention approach/intensity:** Not applicable **Assessment of dietary adherence:** Not applicable **Physical activity:** Not applicable							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Pohl (2009)		**Prescribed intakes**						
	[1] Low CHO high MUFA	1350	37	18	45 [MUFA 32]	NR	NR	NR
	[2] Standard formula	1350	52	18	30 [MUFA 17]	NR	NR	NR
		Reported intakes						
	[1] Low CHO high MUFA	1350	37	18	45 [MUFA 32]	NR	NR	NR
	[2] Standard formula	1350	52	18	30 [MUFA 17]	NR	NR	NR
	Food-based dietary advice: Not applicable **Intervention approach/intensity:** Not applicable **Assessment of dietary adherence:** Not applicable **Physical activity:** Not applicable							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Rock (2014)		**Prescribed intakes**						
	[1] Lower fat	1200 to 2000	60	20	20	>230	NR	NR
	[2] Lower CHO	1200 to 2000	45	25	30	NR	NR	NR
	[3] Usual care	NR	NR	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Lower fat	NR	NR	NR	NR	NR	NR	NR
	[2] Lower CHO	NR	NR	NR	NR	NR	NR	NR
	[3] Usual care	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: In groups 1 and 2, diet meal plans and strategies to reduce energy density of the diet, such as incorporating vegetables and water-rich foods in meals and snacks, were encouraged. **Intervention approach/intensity:** 1:1 sessions/weekly (1 hour) during the first 9 months after which participants had the option to move from weekly to bi-weekly or monthly consultations. **Assessment of dietary adherence:** NR **Physical activity:** Increased physical activity encouraged, with goal of 30 minutes of activity on ≥5 days/week. At 6 months, participants in both weight loss groups but not in usual care group reported increased moderate/vigorous physical activity of 1.5 hours more than baseline levels or than usual care group ($p<0.001$ for each). Participants in all 3 groups had lower recovery heart rates after the step test at 6 m than at baseline ($p<0.001$).							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Samaha (2003)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	30	NR	NR
	[2] Low fat	NR	NR	NR	30	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1630 (894) [SD]	37 (18) [SD]	22 (9) [SD]	41 (16) [SD]	NR	NR	NR
	[2] Low fat	1576 (760) [SD]	51 (15) [SD]	16 (6) [SD]	33 (14) [SD]	NR	NR	NR
	Food-based dietary advice: Group 1: vegetables and fruits with high ratios of fibre to CHO were recommended. Group 2: NR **Intervention approach/intensity:** Group sessions/weekly (2 hours) for 4 weeks followed by monthly 1 hour sessions for 5 additional months. **Assessment of dietary adherence:** 24-hour recall. Authors commented 'the high dropout rate and the small overall weight loss demonstrate that dietary adherence was relatively low in both diet groups'. **Physical activity:** No specific exercise programme recommended.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Saslow (2014)		**Prescribed intakes**						
	[1] Very low CHO, high fat, non-calorie restricted	NR	NR	NR	NR	20 to 50	NR	NR
	[2] Medium CHO, low fat, calorie-restricted, CHO counting diet	NR	45 to 50	NR	NR	165	NR	NR
		Reported intakes						
	[1] Very low CHO, high fat, non-calorie restricted	1693.7 (569.1) [SD]	14.4 (11.9) [SD]	24.2 (6.1) [SD]	58.0 (8.6) [SD]	57.8 (41.5) [SD]	105.7 (51.7) [SD]	110.2 (40.6) [SD]
	[2] Medium CHO, low fat, calorie-restricted, CHO counting diet	1380.8 (527.6) [SD]	40.7 (9.3) [SD]	20.5 (6.8) [SD]	35.1 (8.7) [SD]	138.5 (54.7) [SD]	67.9 (27.9) [SD]	56.1 (30.1) [SD]
	Food-based dietary advice: Group 1: participants taught to count CHOs using 15 g of CHO as a unit. Provided with specific suggestions for amount of CHO units that should be eaten at each of 3 meals and 2 snacks. Most participants asked to eat 3 CHO units/meal and 1 per snack. Group 2: NR **Intervention approach/intensity:** Group sessions/weekly 2-hour meetings (12 weeks); followed by 3 (2 hour) meetings every 2 weeks; and 4 (1.5 hour) every 2 months. **Assessment of dietary adherence:** 24-hour recall. **Physical activity:** Unclear. 3 classes discussed importance of sleep and exercise. Assessed physical activity using version of International Physical Activity Questionnaire. Participants asked about 3 types of physical activity (vigorous, moderate and walking) over “last 7 days”. Using both total amount of activity and number of activity sessions, participants categorised as having low, moderate or high (3) levels of regular physical activity.							

First author (year)	**Intervention groups**	**Energy (kcal)**	**CHO** (% TE)	**Protein** (% TE)	**Fat** [SFA, PUFA, MUFA] (% TE)	**CHO** (g)	**Protein** (g)	**Fat** [SFA, PUFA, MUFA] (g)
Sato (2017)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	130	NR	NR
	[2] Calorie-restricted	NR	50 to 60	NR	NR	NR	1.0 to 1.2 g/kg BW	NR
		Reported intakes						
	[1] Low CHO	1371 (1161 to 1573) [median (IQR)]	43.5	NR	NR	149 (126 to 167) [median (IQR)]	64 (51 to 74) [median (IQR)]	52 (40 to 65) [SFA 15.8 (10.0 to 20.8), PUFA 10.9 (9.7 to 13.0), MUFA 18.8 (14.5 to 24.6)] [median (IQR)]
	[2] Calorie-restricted	1605 (1295 to 1847) [median (IQR)]	49.3	NR	NR	198 (161 to 234) [median (IQR)]	63 (57 to 73) [median (IQR)]	52 (43 to 60) [SFA 14.1 (10.6 to 16.4), PUFA 10.9 (8.7 to 14.3), MUFA 18.9 (15.0 to 22.8)] [median (IQR)]
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/30 minutes at 0, 1, 2, 4 and 6 months.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
	Assessment of dietary adherence: 3-day weighed/measured food record. Authors comment 'more patients of LCD group withdrew from study compared to CRD group, suggesting that adherence to LCD is difficult in some patients'. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Shai (2008)		**Prescribed intakes**						
	[1] Low CHO, non-restricted calorie	NR	NR	18	30	120	NR	NR
	[2] Mediterranean, restricted calorie	1500 to 1800	NR	NR	<35	NR	NR	NR
	[3] Low fat, restricted calorie	NR	NR	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Low CHO, non-restricted calorie	NR	40.4 (7.1) [SD]	21.8 (3.9) [SD]	39.1 (5.5) [SFA 12.3 (3.2)] [SD]	NR	NR	NR
	[2] Mediterranean, restricted calorie	NR	50.2 (8.6) [SD]	18.8 (3.5) [SD]	33.1 (5.5) [SFA 9.6 (2.2)] [SD]	NR	NR	NR
	[3] Low fat, restricted calorie	NR	50.7 (5.7) [SD]	19.0 (3.2) [SD]	30.0 (3.9) [SFA 9.6 (1.8)] [SD]	NR	NR	NR
	Food-based dietary advice: Group 1: participants counselled to choose vegetarian sources of fat and protein and to avoid trans-fat. Group 2: Mediterranean diet rich in vegetables and low in red meat (poultry and fish replacing beef and lamb). Main sources of added fat were 30 to 45 g olive oil and nuts (5 to 7 nuts, <20 g/d). Group 3: participants counselled to consume low-fat grains, vegetables, fruits and legumes and to limit consumption of additional fats, sweets and high-fat snacks. **Intervention approach/intensity:** Group sessions/weeks 1, 3, 5, 7 and thereafter at 6-week intervals, for a total of 18 sessions of 90 minutes each; 6 times during the 2-year intervention dietitian conducted 10 to 15 minutes motivational telephone call with participants having difficulty with adhering to diet. **Assessment of dietary adherence:** FFQ at baseline, 6, 12, 24 months. Subgroup of participants completed 2 repeated 24-hour dietary recalls to verify absolute intake. Overall rate of adherence was 95.4% at 12 months and 84.6% at 24 months. The 24							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
	months adherence rates were 90.4% in low-fat group, 85.3% in Mediterranean diet group and 78.0% in low CHO group (p=0.04 for comparison among diet groups). **Physical activity:** Assessed by validated questionnaire. Transformed physical-activity scores into metabolic equivalents per week according to amount of time spent in various forms of exercise per week, weighted in terms of its level of intensity. The amount of physical activity increased significantly from baseline in all groups, with no significant difference among groups in the amount of increase.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Shirai (2013)		**Prescribed intakes**						
	[1] Formula diet	NR	52	18	30	NR	NR	NR
	[2] Conventional	NR	60	15	25	NR	NR	NR
		Reported intakes						
	[1] Formula diet	1386 (210) [SD]	47 (8.2) [SD]	21 (3.2) [SD]	31 (6.4) [SD]	164 (26.8) [SD]	73.4 (8.6) [SD]	48.5 (12.9) [SD]
	[2] Conventional	1574 (299) [SD]	54 (12) [SD]	15.8 (4.1) [SD]	32.9 (4.1) [SD]	212 (46.7) [SD]	62.3 (14) [SD]	53.1 (8.3) [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/every 4 weeks. **Assessment of dietary adherence:** 3-day food diary for each 2-week period. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Stern (2004)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	<30	NR	NR
	[2] Conventional	NR	NR	NR	<30	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1462 (776) [SD]	32.8	NR	NR	120 (93) [SD]	73 (34) [SD]	93 (117) [SFA 19 (20)] [SD]
	[2] Conventional	1822 (1008) [SD]	50.5	NR	NR	230 (150) [SD]	74 (50) [SD]	69 (48) [SFA 17 (15)] [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/weekly for 4 weeks followed by 11 monthly sessions. **Assessment of dietary adherence:** 24-hour recall. Authors note that their 'findings are limited by a high dropout rate (34%) and by suboptimal dietary adherence of the enrolled persons'. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Strychar (2009)		**Prescribed intakes**						
	[1] Low CHO, high MUFA	NR	43 to 46	NR	37 to 40 [SFA <10, MUFA 20]	NR	NR	NR
	[2] High CHO, low fat	NR	54 to 57	NR	27 to 30 [SFA <10, MUFA 10]	NR	NR	NR
		Reported intakes						
	[1] Low CHO, high MUFA	NR	NR	NR	NR	NR	NR	NR
	[2] High CHO, low fat	NR	NR	NR	NR	NR	NR	NR
	Food-based dietary advice: Group 1: fewer starch and more fat choices in the form of olive oil. Group 2: NR **Intervention approach/intensity**: NR **Assessment of dietary adherence**: NR **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Tay (2014)		**Prescribed intakes**						
	[1] Low CHO, high unsaturated, low saturated fat	NR	14	28	58 [SFA <10%; MUFA 35%; PUFA 13%]	<50	NR	NR
	[2] High CHO, low fat	NR	53	17	<30 [SFA <10%; MUFA 15%, PUFA 9%]	NR	NR	NR
		Reported intakes						
	[1] Low CHO, high unsaturated, low saturated fat	1563 (225) [SD]	13.9 (1.6) [SD]	26.7 (1.3) [SD]	54.1 (2.6) [SFA 10.0 (0.9), PUFA 12.2 (1.1), MUFA 30.4 (1.8)] [SD]	56.7 (8.0) [SD]	102.8 (14.7) [SD]	96.5 (16.5) [SD]
	[2] High CHO, low fat	1587 (171) [SD]	50.1 (2.0) [SD]	18.8 (0.9) [SD]	24.5 (2.5) [SFA 7.5 (1.1), PUFA 4.1 (0.6), MUFA 11.5 (1.3)] [SD]	204.9 (22.8) [SD]	73.6 (8.3) [SD]	44.3 (7.4) [SD]
	Food-based dietary advice: Group 1: 30 g high-fibre, low GI cereal; 1 crispbread; 250 g lean chicken, pork, fish, red meat (3-4 times/week); 4g almonds and 20g pecans; 3 cups low-starch vegetables (exclude potato/sweet potato/corn); 200 ml skim (<1% fat) milk; 100g diet yogurt; 20g cheese; 30g margarine/oil (MUFA, eg, canola oil/margarine). Group 2: 40g high-fibre, low GI cereal; 5 crispbread; ½ cup cooked pasta/rice/potato; 2 slices wholegrain bread (70g); 80g lean chicken, pork, red meat (4 times/week); 80g fish (2 times/week); 80g legumes (1 time/week); 3 cups vegetables; 400g fruit; 250 ml reduced-fat (1 to 2%) milk; 150 g reduced-fat yogurt; 20 g cheese; 25 g margarine/oil (MUFA, eg, canola oil/margarine). **Intervention approach/intensity:** 1:1 sessions/every 2 weeks for 12 weeks and monthly thereafter.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
	Assessment of dietary adherence: Random sample of 7 consecutive days of daily weighed food records for every 14-day period. Authors note that 'reported dietary intakes were consistent with diet prescriptions'. **Physical activity:** Exercise session attendance and accelerometry; participants undertook 60-minute classes of professionally supervised exercise in a circuit training format 3 days/week that incorporated moderate intensity aerobic/resistance exercises (encouraged to make-up any missed sessions). Physical activity assessed with 7 consecutive days of triaxial accelerometry. Exercise session attendance similar between groups. Mean activity count and time spent in moderate to vigorous physical activity from accelerometry increased similarly in both groups.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Tay (2015)		**Prescribed intakes**						
	[1] Low CHO, high unsaturated, low saturated fat	NR	14	28	58 [SFA <10, PUFA 13, MUFA 35]	<50	NR	NR
	[2] High CHO, low fat	NR	53	17	30 [SFA <10, PUFA 9, MUFA 15]	NR	NR	NR
		Reported intakes						
	[1] Low CHO, high unsaturated, low saturated fat	1700 (335) [SD]	16.6 (2.5) [SD]	25.6 (2.1) [SD]	52.5 (3.0) [SFA 11.0 (1.4), PUFA 11.1 (1.4), MUFA 28.8 (2.3)] [SD]	74.0 (18.1) [SD]	106.1 (18.9) [SD]	101.5 (23.5) [SFA 21.2 (5.5)] [SD]
	[2] High CHO, low fat	1737 (309) [SD]	49.0 (3.2) [SD]	18.4 (1.4) [SD]	26.1 (3.5) [SFA 8.5 (1.5), PUFA 4.2 (0.8), MUFA 12.0 (1.9)] [SD]	217.6 (35.1) [SD]	78.5 (14.8) [SD]	51.8 (14.1) [SFA 16.8 (4.8)] [SD]
	Food-based dietary advice: See Tay (2014) above. **Intervention approach/intensity:** See Tay (2014) above. **Assessment of dietary adherence:** Random sample of 7 consecutive days of daily food records for every 14-day period. **Physical activity:** Advice as above. Mean exercise session attendance similar between groups. Both groups had similar increases in mean activity count and time spent in moderate to vigorous physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Tay (2018)		**Prescribed intakes**						
	[1] Low CHO, high unsaturated, low saturated fat	NR	14	28	58 [SFA <10]	<50	NR	NR
	[2] High CHO, low fat	NR	53	17	30 [SFA <10]	NR	NR	NR
		Reported intakes [Estimated marginal means (95% CI)]						
	[1] Low CHO, high unsaturated, low saturated fat	1707 (1604 to 1811)	19 (17 to 20)	25 (25 to 26)	50 (49 to 52) [SFA 11 (11 to 12), PUFA 11 (10 to 11), MUFA 25 (24 to 26)]	83 (73 to 94) [	105 (100 to 111)	98 (91 to 104) [SFA 22 (20 to 24)]
	[2] High CHO, low fat	1757 (1651 to 1863)	48 (46 to 49)	18 (18 to 19)	27 (26 to 29) [SFA 9 (8 to 10), PUFA 4 (4 to 5), MUFA 11 (10 to 12)]	216 (206 to 227)	79 (73 to 84)	55 (48 to 62) [SFA 18 (16 to 20)]
	Food-based dietary advice: Group 2: processed CHOs and high GI foods were discouraged, with an emphasis on the selection of low glycaemic foods; overall GI of 46. **Intervention approach/intensity:** As above. **Assessment of dietary adherence:** Random sample of 7 consecutive days of daily food records for every 14-day period. Authors note: dietary intakes were consistent with the prescribed diets. **Physical activity:** Advice as above. Physical activity levels were similar between groups. Exercise session attendance was also similar between groups.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Walker (1995)		**Prescribed intakes**						
	[1] Modified fat	NR	40	NR	40 [PUFA:MUFA:SFA 1:2:1]	NR	NR	NR
	[2] High CHO, low fat	NR	59	NR	21 [PUFA:MUFA:SFA 1:1:1]	NR	NR	NR
		Reported intakes						
	[1] Modified fat	1552.5 (95.5) [SE]	40 (0.7) [SE]	22 (0.6) [SE]	36 (0.9) [SFA 11 (0.5), PUFA 5 (0.1), MUFA 20 (0.5)] [SE]	NR	NR	NR
	[2] High CHO, low fat	1504.7 (95.50 [SE]	50 (1.0) [SE]	24 (0.6) [SE]	23 (1.1) [SFA 9 (0.4), PUFA 4 (0.2), MUFA 10 (0.6)] [SE]	NR	NR	NR
	Food-based dietary advice: Unrefined cereals, legumes, fresh fruit and vegetables, non-fat dairy products, very lean meat, and fish. Foods in Group 1 same as in Group 2 except 13% of energy supplied as olive oil and 7% of energy as olive oil based margarine (66.2% C18:l, 10.9% C18:2, 3.2% C18:3 fatty acids, and 14.4% trans fatty acids). The olive oil was used to stir-fry vegetables, as an ingredient in muffins and toasted muesli, or as a dressing. **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Advised to maintain usual physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Walker (1999)		**Prescribed intakes**						
	[1] High MUFA	NR	40	NR	40 [MUFA 20]	NR	NR	NR
	[2] High CHO	NR	60	NR	20	NR	NR	NR
		Reported intakes						
	[1] High MUFA	1504.7 (453.8) [SD]	43.4 (4.9) [SD]	21.4 (1.6) [SD]	32.6 (4.7) [SFA 9.8(1.6), PUFA 5.0 (0.9), MUFA 17.7 (4.2)] [SD]	NR	NR	NR
	[2] High CHO	1480.8 (477.70 [SD]	51.6 (5.5) [SD]	24.5 (3.0) [SD]	22.1 (5.5) [SFA 9.3 (2.5), PUFA 3.6 (1.0), MUFA 9.2 (2.3)] [SD]	NR	NR	NR
	Food-based dietary advice: High-MUFA 5 ± 7 olives or 10 ± 20 g raw nuts, or 30 ± 60 g avocado were prescribed daily. High CHO diet was restricted in total fat intake and enriched by wholemeal or wholegrain bread, potatoes, rice and pasta and with whole grain breakfast cereals. **Intervention approach/intensity:** NR **Assessment of dietary adherence:** NR **Physical activity:** Advised to maintain usual physical activity.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Watson (2016)		**Prescribed intakes**						
	[1] High protein	NR	33	32	30 [SFA <10]	130-230	NR	NR
	[2] High CHO	NR	51	22	22 [SFA <10]	NR	NR	NR
		Reported intakes						
	[1] High protein	1736.9 (239.5) (phase 2); 1490.4 (147.5) (phase 1) [SEM]	33.6 (3.2) [SEM]	28.5 (2.8) [SEM]	31.6 (2.9) [SFA: 36.0 (4.4), PUFA: 17.7 (3.1), MUFA: 46.3 (2.5) 5 of total fat] [SEM]	149.2 (18.8) [SEM]	121.3 (19.6) [SEM]	62.2 (10.4) [SEM]
	[2] High CHO	1666.3 (248.1) phase 2; 1420.9 (207.0), phase 1 [SEM]	47.2 (4.5) [SEM]	20.1 (1.5) [SEM]	25.1 (3.6) [SFA: 33.3 (3.9), PUFA: 21.2 (4.2), MUFA: 45.5 (3.8) 5 of total fat] [SEM]	199.3 (23.6) [SEM]	82.1 (12.5) [SEM]	47.8 (11.7) [SEM]
	Food-based dietary advice: Provided with core foods that included fresh lean pork, breakfast cereal, mixed grain bread, fat-reduced cheese (Group 1 only), and raw almonds (Group 1 only). **Intervention approach/intensity:** 1:1 sessions/every 2 weeks. Provided with core study foods corresponding to their assigned dietary pattern. **Assessment of dietary adherence:** Daily semi-quantitative food records. Analysis based on 7 consecutive days from every 2-weekly food record. Authors comment: Based on dietary data collected, participants achieve good compliance to their allocated dietary prescription.							

First author (year)	**Intervention groups**	**Energy (kcal)**	**CHO** (% TE)	**Protein** (% TE)	**Fat** [SFA, PUFA, MUFA] (% TE)	**CHO** (g)	**Protein** (g)	**Fat** [SFA, PUFA, MUFA] (g)
	Physical activity: Asked to undertake minimum 30 minutes moderate aerobic exercise 5 times/week (150 mins/wk). Participants completed physical activity logs to monitor compliance. Both groups exceeded their requirements with no significant differences between groups.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Westman (2008)		**Prescribed intakes**						
	[1] Low CHO, ketogenic	NR	NR	NR	NR	<20	NR	NR
	[2] Low GI, reduced calorie	NR	55	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Low CHO, ketogenic	1550 (440) [SD]	13 [SD]	28 [SD]	59 [SD]	49 (33) [SD]	108 (33) [SD]	101 (35) [SD]
	[2] Low GI, reduced calorie	1335 (372) [SD]	44 [SD]	20 [SD]	36 [SD]	149 (46) [SD]	67 (20) [SD]	55 (23) [SD]
	Food-based dietary advice: Group 1: Unlimited amounts of animal foods (ie, meat, fish) and eggs; limited amounts hard cheese (4oz/day), fresh cheese (eg, cottage/ricotta, 2oz/day), salad vegetables (2 cups/day), and non-starchy vegetables (1 cup/day). Encouraged to drink at least 6 glasses of permitted fluids daily. Drinking bouillon dissolved in water recommended 2 to 3 times/day during first 2 weeks to reduce possible side effects. Group 2: instructed to follow low GI diet. **Intervention approach/intensity:** Group sessions/every week for 3 months, then every other week for 3 months. **Assessment of dietary adherence:** 5-day food diary (5 consecutive days, including weekend) at baseline and weeks 4, 12, 24. **Physical activity:** Encouraged to exercise for 30 minutes at least 3 times/week. Adherence with exercise recommendations measured by self-report. After 24 weeks no difference in self-reported exercise between the 2 groups.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Wolever (2008)		**Prescribed intakes**						
	[1] Low CHO, high MUFA	NR	NR	NR	Total fat intake increased by ~10%	NR	NR	NR
	[2] Low GI, high CHO	NR	20 to 25	NR	NR	NR	NR	NR
	[3] High GI, high CHO	NR	20 to 25	NR	NR	NR	NR	NR
		Reported intakes						
	[1] Low CHO, high MUFA	2020 (57) [SD]	39.3 (0.7) [SD]	19.1 (0.4) [SD]	40.1 (0.6) [SFA 10.8 (0.3), PUFA 8.2 (0.2), MUFA 18.3 (0.3)] [SD]	NR	NR	NR
	[2] Low GI, high CHO	1800 (50) [SD]	51.9 (0.9) [SD]	20.6 (0.4) [SD]	26.5 (0.8) [SFA 8.2 (0.4), PUFA 5.1 (0.2), MUFA 10.7 (0.4)] [SD]	NR	NR	NR
	[3] High GI, high CHO	1890 (48) [SD]	46.5 (0.9) [SD]	20.4 (0.4) [SD]	30.8 (0.7) [SFA 10.2 (0.4), PUFA 5.5 (0.2), MUFA 12.3 (0.3)] [SD]	NR	NR	NR
	Food-based dietary advice: Group 1: key foods consisted of olive or canola oils or spreads, nuts, and other foods low in sat fats and high in MUFAs and known to be associated with reduced risks of diabetes and CVD. **Intervention approach/intensity:** 1:1 sessions/every 2 months (5 times). **Assessment of dietary adherence:** 3-day food diaries; key food diaries. **Physical activity:** NR							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Wycherley (2010)		**Prescribed intakes**						
	[1] High protein	NR	43	33	22	130 to 230	NR	NR
	[2] Energy-restricted standard CHO	NR	53	19	26	NR	NR	NR
		Reported intakes						
	[1] High protein	1510.8 (182.4) [SD]	47.4 (1.6) [SD]	32.3 (2.8) [SD]	17.7 (3.0) [SFA 33.9 (5.0), PUFA 22.3 (3.6), MUFA 43.9 (4.1)] [SD]	176.3 (23.7) [SD]	119.0 (7.8) [SD]	30.5 (8.2) [SD]
	[2] Energy-restricted standard CHO	1500.5 (154.9) [SD]	53.6 (2.6) [SD]	18.6 (0.9) [SD]	22.6 (3.0) [SFA 34.1 (5.5), PUFA 19.8 (4.5), MUFA 46.1 (6.6)] [SD]	197.4 (16.3) [SD]	68.4 (5.9) [SD]	38.5 (7.7) [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/every 2 weeks. Key foods representative of each diets macronutrient profile supplied every 2 weeks. **Assessment of dietary adherence:** 7-day food diary (semiquantitative, weighted) every 2 weeks. Author comments: Based on the food records, participants showed good compliance with the prescribed diets. **Physical activity:** 2 dietary arms and exercise were also included in study but not included in analysis of individual studies.							

First author (year)	Intervention groups	Energy (kcal)	CHO (% TE)	Protein (% TE)	Fat [SFA, PUFA, MUFA] (% TE)	CHO (g)	Protein (g)	Fat [SFA, PUFA, MUFA] (g)
Yamada (2014)		**Prescribed intakes**						
	[1] Low CHO	NR	NR	NR	NR	70 to 130	NR	NR
	[2] Conventional calorie-restricted	NR	50 to 60	<20	<25	NR	NR	NR
		Reported intakes						
	[1] Low CHO	1634 (531) [SD]	29.8 (12.5) [SD]	25.3 (7.3) [SD]	45.4 (8.9) [SD]	125.7 (71.9) [SD]	100.4 (36.6) [SD]	82.1 (33.0) [SD]
	[2] Conventional calorie-restricted	1610 (387) [SD]	51.0 (4.6) [SD]	16.6 (2.8) [SD]	32.3 (5.2) [SD]	202.9 (42.0) [SD]	67.6 (21.2) [SD]	58.5 (20.7) [SD]
	Food-based dietary advice: NR **Intervention approach/intensity:** 1:1 sessions/every 2 months. **Assessment of dietary adherence:** 3-day diet record. **Physical activity:** NR							

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Annex 7: Overlap of primary publications included in 8 eligible systematic reviews with meta-analyses, grouped by outcome

Table A7.1A: Body weight (shorter term; ≥3 to 6 m)

First author (year)	van Zuuren (2018) 4 to 6 m	Korsmo-Haugen (2018) 3 to 6 m	Sainsbury (2018) 3 m	Sainsbury (2018) 6 m	Huntriss[1] (2018) 3m	Snorgaard[2] (2017) 3 to 6 m	Fan (2016) 3 m	Fan (2016) 6 m	Naude (2014) 3 to 6 m	Meng (2017) 3 to 6m	Overlap
1 Brehm (2009)			X	X							2
2 Brinkworth (2004)									X		1
3 Brunerova (2007)			X				X				2
4 Daly (2006)		X	X		X					X	4
5 Davis (2009)	X		X	X	X	X					5
6 De Bont (1981)	X										1
7 Goday (2016)	X										1
8 Goldstein (2011)										X	1
9 Guldbrand (2012)	X			X		X			X		4
10 Iqbal (2009)						X					1
11 Jenkins (2014)		X									1
12 Jonasson (2014)		X									1
13 Krebs (2012)				X		X			X		3
14 Larsen (2011)			X			X			X		3
15 Luger (2013)		X	X								2
16 McLaughlin (2007)		X									1
17 Nielsen (2005)	X							X			2
18 Parker (2002)			X						X		2
19 Samaha (2003)								X			1
20 Saslow (2014)			X			X				X	3
21 Tay (2014)	X					X				X	3
22 Watson (2016)			X	X							2

23	Westman (2008)		X	X	X	X						4
24	Wolever (2008)			X	X							2
25	Wycherley (2010)			X								1
26	Yamada (2014)	X	X		X		X		X		X	6
	Total number	7	7	12	8	3	8	1	3	5	5	

[1] considered 5 RCTs that examined the effect of LCDs on shorter-term weight change (3 m) but only specified 3 RCTs.

[2] considered 8 RCTs that examined the effect of LCDs on shorter-term weight change (3 and 6 m). Of these, 7 RCTs were included in a MA but were not specified.

Table A7.1B: Body weight (longer term; ≥12 m)

First author (year)	van Zuuren (2018) ≥12 m	Korsmo-Haugen (2018) >12 m	Huntriss (2018) 12m	Sainsbury (2018) 12 m	Snorgaard (2017) ≥12 m	Fan (2016) ≥12 m	Naude (2014) 12 to 24m	Overlap
1 Brehm (2009)				X				1
2 Brinkworth (2004)		X		X			X	3
3 Davis (2009)	X	X	X	X		X		5
4 Elhayany (2010)	X	X		X	X	X		5
5 Esposito (2009)			X					1
6 Facchini 2003		X						1
7 Goldstein (2011)		X	X					2
8 Guldbrand (2012)	X	X	X	X	X	X	X	8
9 Hockaday (1978)	X							1
10 Iqbal (2009)					X			1
11 Krebs (2012)		X		X	X		X	4
12 Larsen (2011)		X	X	X	X		X	5
13 Mayer (2014)			X					1
14 Pedersen (2014)		X		X				2
15 Stern (2004)						X		1
16 Tay (2015)				X				1
17 Tay (2018)	X							1
18 Wolever (2008)	X	X		X	X			4
Total number	6	10	6	10	6	4	4	

Table A7.2A: HbA1c (shorter term; ≥3 to 6 m)

First author (year)	van Zuuren (2018) 4 to 6 m	Korsmo-Haugen (2018) 3 to 6 m	Sainsbury (2018) 3 m	Sainsbury (2018) 6 m	Snorgaard (2017) 3 to 6 m	Fan (2016) 3 m	Fan (2016) 6 m	Naude (2014) 3 to 6 m	Overlap
1 Brehm (2009)			X	X					2
2 Brinkworth (2004)								X	1
3 Brunerova (2007)			X						1
4 Daly (2006)		X	X			X			3
5 Davis (2009)	X		X	X	X				3
6 Fabricatore (2011)				X					1
7 Guldbrand (2012)	X			X	X			X	3
8 Iqbal (2009)					X				1
9 Jenkins (2014)		X							1
10 Jonasson (2014)		X							1
11 Krebs (2012)				X	X			X	3
12 Larsen (2011)			X		X			X	3
13 Luger (2013)		X	X						2
14 Nielsen (2005)	X						X		1
15 Parker (2002)			X					X	2
16 Samaha (2003)				X			X		2
17 Saslow (2014)			X		X				2
18 Tay (2014)	X				X				1
19 Watson (2016)			X	X					2
20 Westman (2008)		X	X	X					3
21 Wolever (2008)			X	X					2
22 Wycherley (2010)			X						1
23 Yamada (2014)	X	X		X	X		X		4
Total number	5	6	12	10	8	1	3	5	

Table A7.2B: HbA1c (longer term; ≥12 m)

First author (year)	van Zuuren (2018) ≥12 m	van Zuuren (2018) 24 m	Korsmo-Haugen (2018) >12 m	Huntriss (2018) 12 m	Sainsbury (2018) 12 m	Snorgaard (2017) ≥12 m	Fan (2016) ≥12 m	Naude (2014) 12 to 24 m	Overlap
1 Brehm (2009)					X				1
2 Brinkworth (2004)			X		X			X	3
3 Davis (2009)	X		X	X	X	X	X		6
4 Elhayany (2010)	X		X		X	X	X		5
5 Esposito (2009)				X			X		2
6 Fabricatore (2011)					X				1
7 Goldstein (2011)			X	X					2
8 Guldbrand (2012)	X	X	X	X	X	X	X	X	8
9 Iqbal (2009)						X	X		2
10 Krebs (2012)			X		X	X		X	4
11 Larsen (2011)			X	X	X	X		X	5
12 Mayer (2014)				X					1
13 Pedersen (2014)			X		X				2
14 Shai (2008)		X	X						2
15 Stern (2004)					X		X		2
16 Tay (2015)				X	X				2
17 Tay (2018)		X							1
18 Wolever (2008)	X		X		X	X			4
Total number	4	3	10	7	12	7	6	4	

Table A7.3: Fasting blood glucose (shorter and longer term)

First author (year)	van Zuuren (2018) ≥4 to 6 m	van Zuuren (2018) ≥12 m	Overlap
1 de Bont (1981)	X		1
2 Elhayany (2010)		X	1
3 Goday (2016)	X		1
4 Hockaday (1978)		X	1
5 Nielsen (2005)	X		1
6 Shai (2008)	X	X	2
7 Tay (2014)	X		1
8 Tay (2018)		X	1
9 Wolever (2008)		X	1
10 Yamada (2014)	X		1
Total number	6	5	

Table A7.4: Serum total cholesterol (shorter and longer term)

First author (year)	Korsmo-Haugen (2018) 3 to 6 m	Fan (2016) 6 m	Naude (2014) 3 to 6 m	Korsmo-Haugen (2018) >12 m	Huntriss (2018) 12 m	Fan (2016) ≥12 m	Naude (2014) 12 to 24 m	Overlap
1 Brehm (2009)						X		1
2 Brinkworth (2004)			X	X			X	3
3 Davis (2009)		X		X	X	X		4
4 Elhayany (2010)				X		X		2
5 Esposito (2009)					X	X		2
6 Facchini (2003)				X				1
7 Goldstein (2011)				X	X			2
8 Guldbrand (2012)		X	X	X	X	X	X	6
9 Iqbal (2009)		X				X		2
10 Jenkins (2014)	X							1
11 Jonasson (2014)	X							1
12 Krebs (2012)			X	X			X	3
13 Larsen (2011)			X	X	X		X	4
14 Mayer (2014)					X			1
15 McLaughlin (2007)	X							1
16 Parker (2002)			X					1
17 Pedersen (2014)				X				1
18 Samaha (2003)		X						1
19 Stern (2004)						X		1
20 Tay (2015)					X			1
21 Westman (2008)	X							1
22 Wolever (2008)				X				1
Total number	4	4	5	10	7	7	4	

Table A7.5: Serum triacylglycerol (shorter and longer term)

First author (year)	van Zuuren (2018) ≥4 to 6 m	Korsmo-Haugen (2018) 3 to 6 m	Fan (2016) 6 m	Naude (2014) 3 to 6 m	van Zuuren (2018) ≥12 m	Korsmo-Haugen (2018) >12 m	Huntriss (2018) 12 m	Fan (2016) ≥12 m	Naude (2014) 12 to 24 m	Overlap
1 Brinkworth (2004)				X		X			X	3
2 Daly (2006)		X								1
3 Davis (2009)	X		X		X	X	X	X		6
4 de Bont (1981)	X									1
5 Elhayany (2010)					X	X		X		3
6 Esposito (2009)							X	X		2
7 Goday (2016)	X									1
8 Goldstein (2011)						X	X			2
9 Guldbrand (2012)	X		X	X	X	X	X	X	X	8
10 Hockaday (1978)					X					1
11 Iqbal (2009)			X					X		2
12 Jenkins (2014)		X								1
13 Jonasson (2014)		X								1
14 Krebs (2012)						X				1
15 Larsen (2011)				X		X	X		X	4
16 Luger (2013)		X								1
17 Mayer (2014)							X			1
18 McLaughlin (2007)		X								1
19 Parker (2002)				X						1
20 Pedersen (2014)						X				1
21 Samaha (2003)			X							1
22 Stern (2004)								X		1
23 Tay (2014)	X									1
24 Tay (2015)							X			1
25 Tay (2018)					X					1
26 Westman (2008)		X								1
27 Wolever (2008)					X	X				2
28 Yamada (2014)	X	X	X							3
Total number	6	7	5	4	6	9	7	6	3	

Table A7.6: Serum LDL cholesterol (shorter and longer term)

First author (year)	van Zuuren (2018) ≥4-6m	Korsmo-Haugen (2018) 3 to 6 m	Snorgaard (2017) <12 m	Fan (2016) 6 m	Naude (2014) 3 to 6 m	van Zuuren (2018) ≥12 m	Korsmo-Haugen (2018) >12 m	Huntriss (2018) 12 m	Snorgaard (2017) ≥12 m	Fan (2016) ≥12 m	Naude (2014) 12 to 24 m	Overlap
1 Brinkworth (2004)					X		X				X	3
2 Davis (2009)	X		X	X		X	X	X	X	X		8
3 Elhayany (2010)						X	X		X	X		4
4 Facchini (2003)							X					1
5 Goday (2016)	X											1
6 Guldbrand (2012)	X		X	X	X	X	X	X	X	X	X	10
7 Iqbal (2009)			X	X					X	X		4
8 Jenkins (2014)		X										1
9 Jonasson (2014)		X										1
10 Krebs (2012)			X		X		X		X		X	5
11 Larsen (2011)			X		X		X	X	X		X	6
12 Luger (2013)		X										1
13 Mayer (2014)								X				1
14 McLaughlin (2007)		X										1
15 Parker (2002)					X							1
16 Pedersen (2014)							X					1
17 Samaha (2003)				X								1
18 Saslow (2014)			X									1
19 Stern (2004)										X		1
20 Tay (2014)	X		X									2
21 Tay (2015)								X				1
22 Tay (2018)						X						1
23 Westman (2008)		X										1
24 Wolever (2008)						X	X		X			3
25 Yamada (2014)	X	X	X	X								4
Total number	5	6	8	5	5	5	9	5	7	5	4	

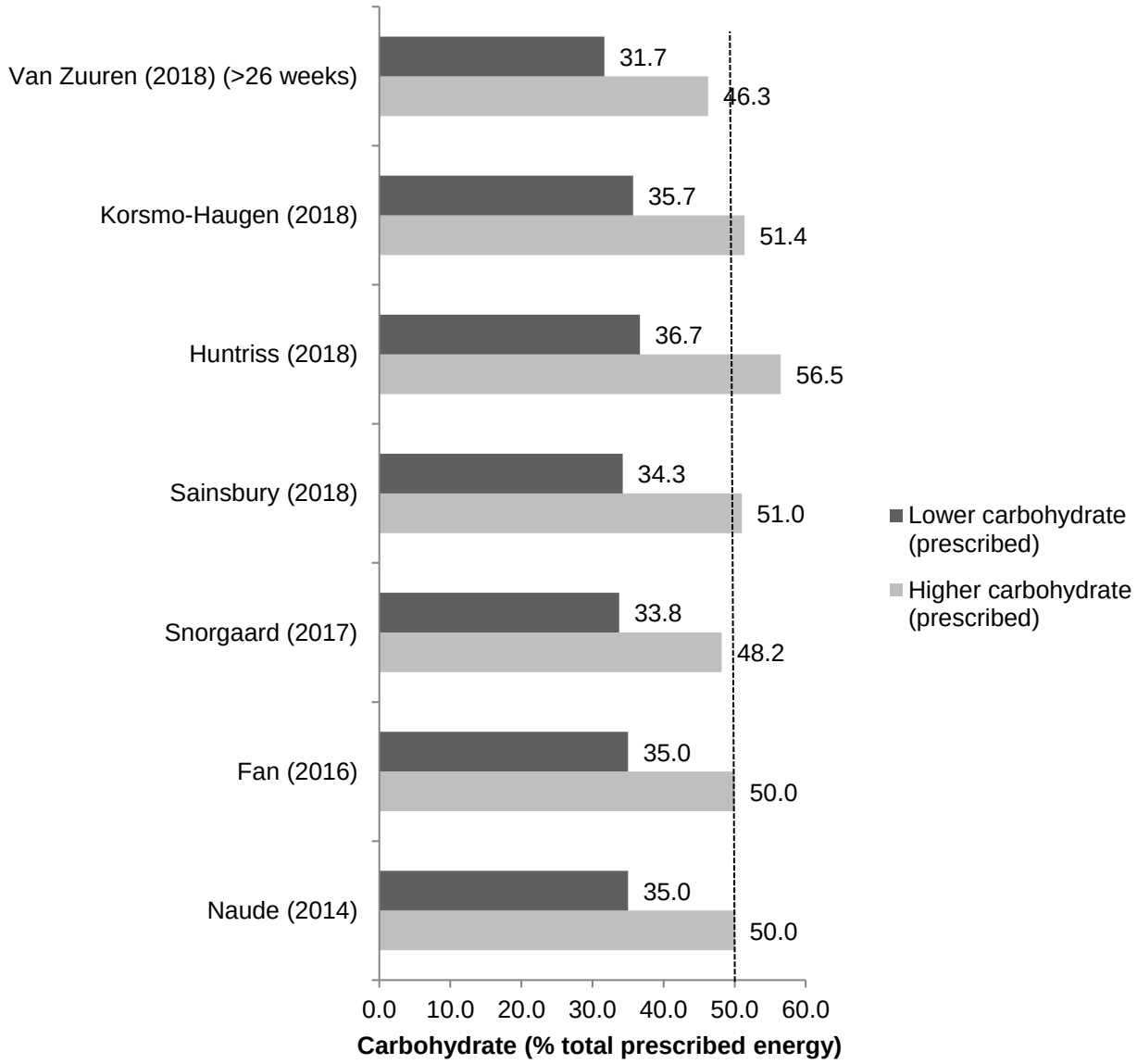
Table A7.7: Serum HDL cholesterol (shorter and longer term)

First author (year)	van Zuuren (2018) ≥4 to 6 m	Korsmo-Haugen (2018) 3 to 6 m	Fan (2016) 6 m	Naude (2014) 3 to 6 m	van Zuuren (2018) ≥12 m	Korsmo-Haugen (2018) >12 m	Huntriss (2018) 12 m	Fan (2016) ≥12 m	Naude (2014) 12 to 24 m	Overlap
1 Brinkworth (2004)				X		X			X	3
2 Davis (2009)	X		X		X	X	X	X		6
3 de Bont (1981)	X									1
4 Elhayany (2010)					X	X		X		3
5 Esposito (2009)							X	X		2
6 Facchini (2003)						X				1
7 Goday (2016)	X									1
8 Goldstein (2011)						X	X			2
9 Guldbrand (2012)	X		X	X	X	X	X	X	X	8
10 Iqbal (2009)			X					X		2
11 Jenkins (2014)		X								1
12 Jonasson (2014)		X								1
13 Krebs (2012)				X		X			X	3
14 Larsen (2011)				X		X	X		X	4
15 Luger (2013)		X								1
16 Mayer (2014)							X			1
17 McLaughlin (2007)		X								1
18 Parker (2002)				X						1
19 Pedersen (2014)						X				1
20 Samaha (2003)			X							1
21 Stern (2004)								X		1
22 Tay (2014)	X									1
23 Tay (2015)							X			1
24 Tay (2018)					X					1
25 Westman (2008)		X								1
26 Wolever (2008)					X	X				2
27 Yamada (2014)	X	X	X							3
Total number	6	6	5	5	5	10	7	6	4	

Annex 8: Comparison of macronutrient and energy intakes between lower and higher carbohydrate groups in the 8 eligible systematic reviews with meta-analyses

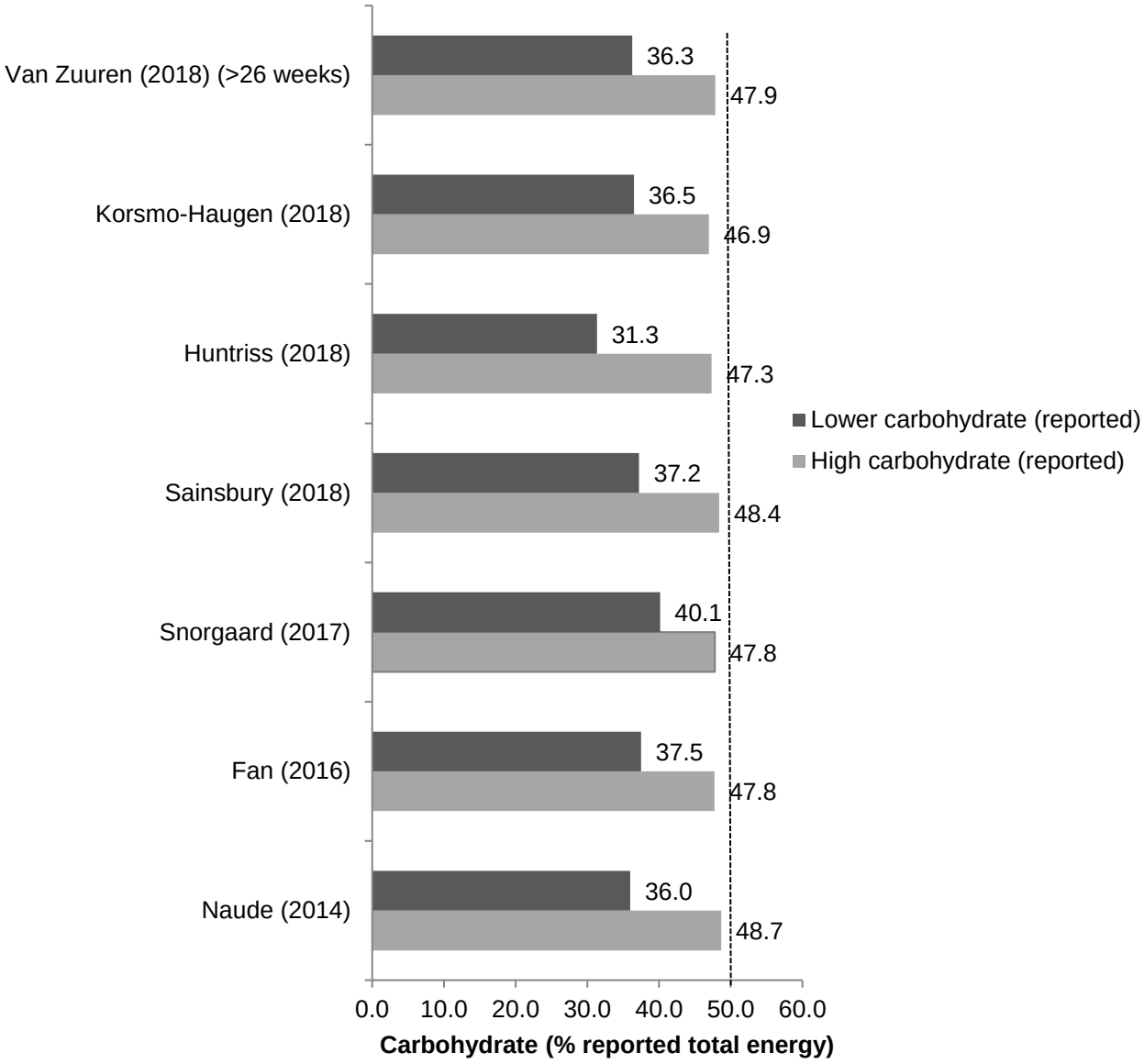
Data from meta-analyses for outcome of body weight in longer-term studies (≥12 months) (Figures A8.1 to A8.10)

Figure A8.1: Average prescribed intakes of carbohydrate in lower and higher carbohydrate groups (% of total prescribed energy)



The vertical dashed line (---) represents the DRV for total carbohydrate (approximately 50% of total dietary energy) (SACN, 2015).

Figure A8.2: Average reported intakes of carbohydrate in lower and higher carbohydrate groups (% of total reported energy)



The vertical dashed line (---) represents the DRV for total carbohydrate (approximately 50% of total dietary energy) (SACN, 2015).

Figure A8.3: Difference in average prescribed carbohydrate intakes in lower and higher carbohydrate groups versus difference in average reported carbohydrate intakes in lower and higher carbohydrate groups

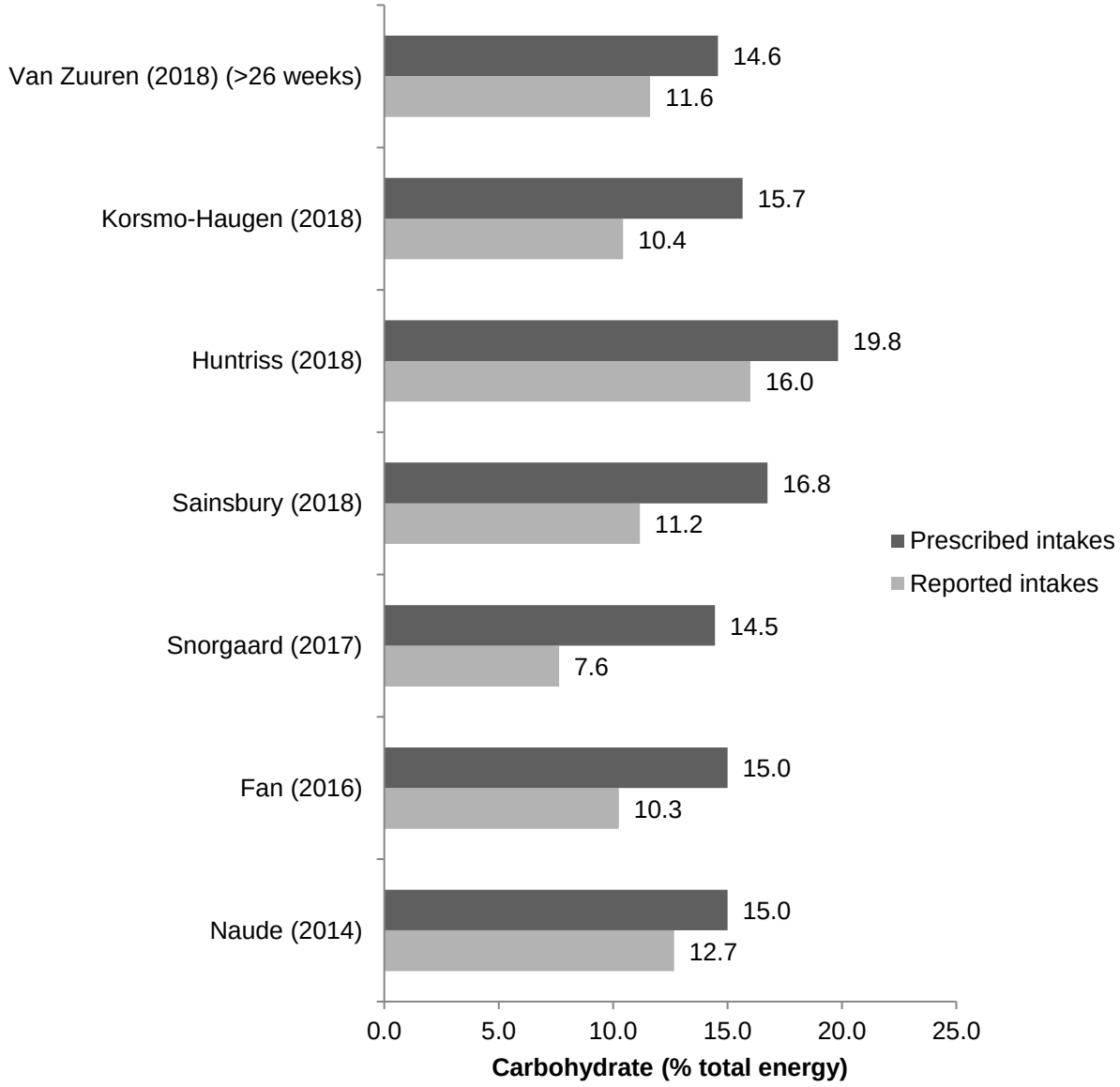
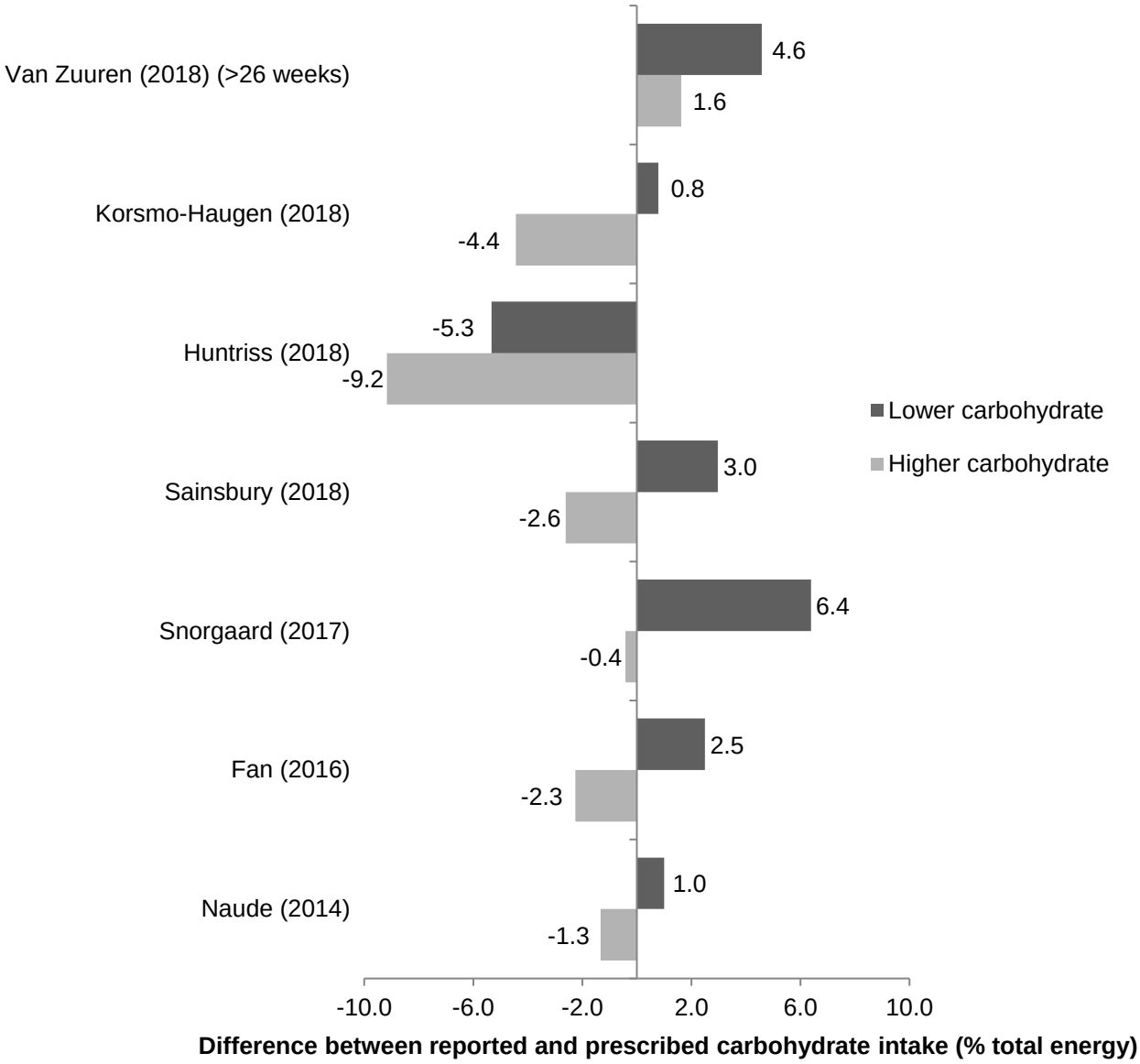


Figure A8.4: Adherence to prescribed intakes of carbohydrate in the lower and higher carbohydrate groups



Positive and negative values indicate that the average reported intake was above or below the average prescribed intake, respectively.

Figure A8.5: Average reported intakes of carbohydrate, fat and protein in lower carbohydrate groups

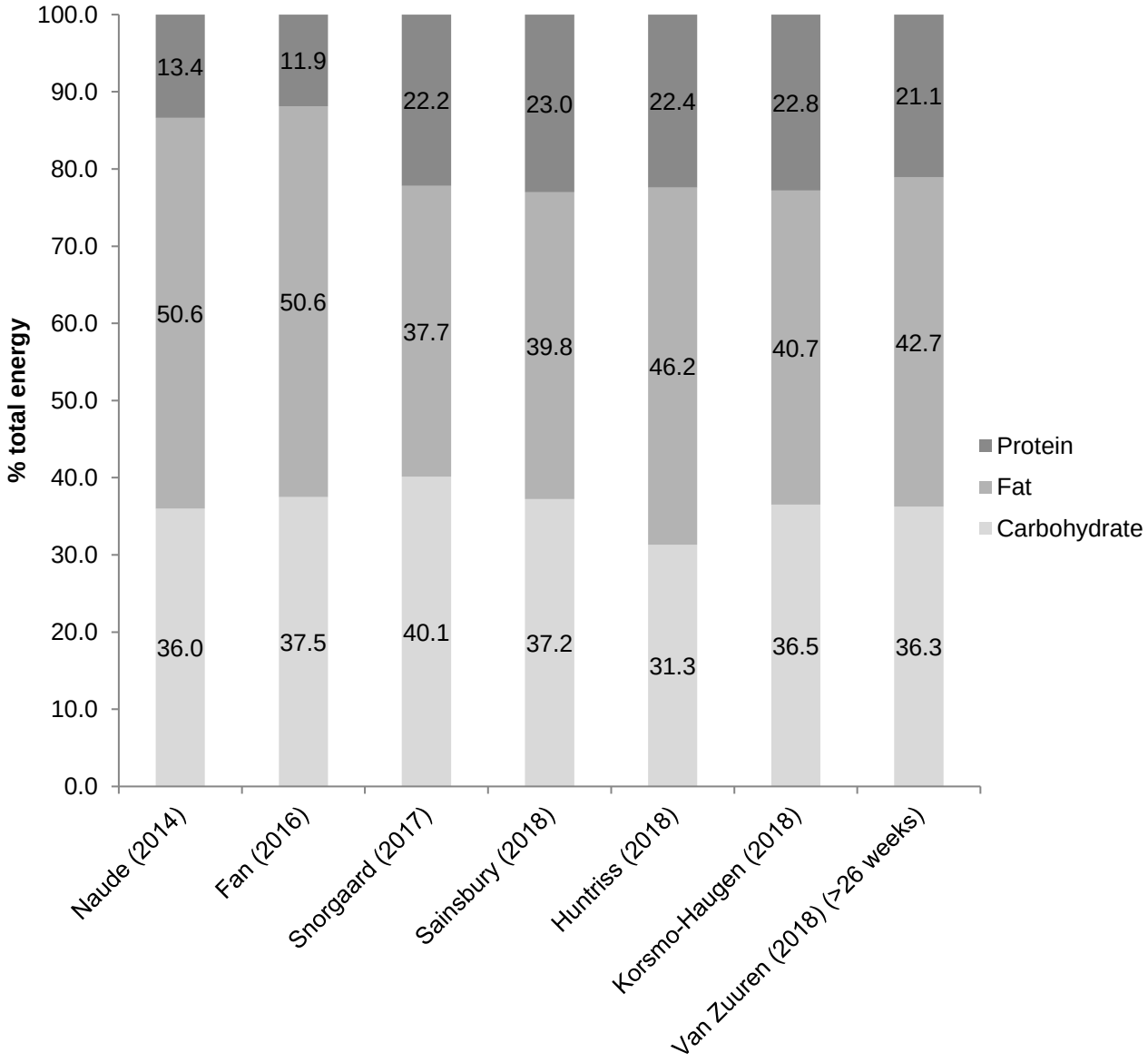


Figure A8.6: Average reported intakes of carbohydrate, fat and protein in higher carbohydrate groups

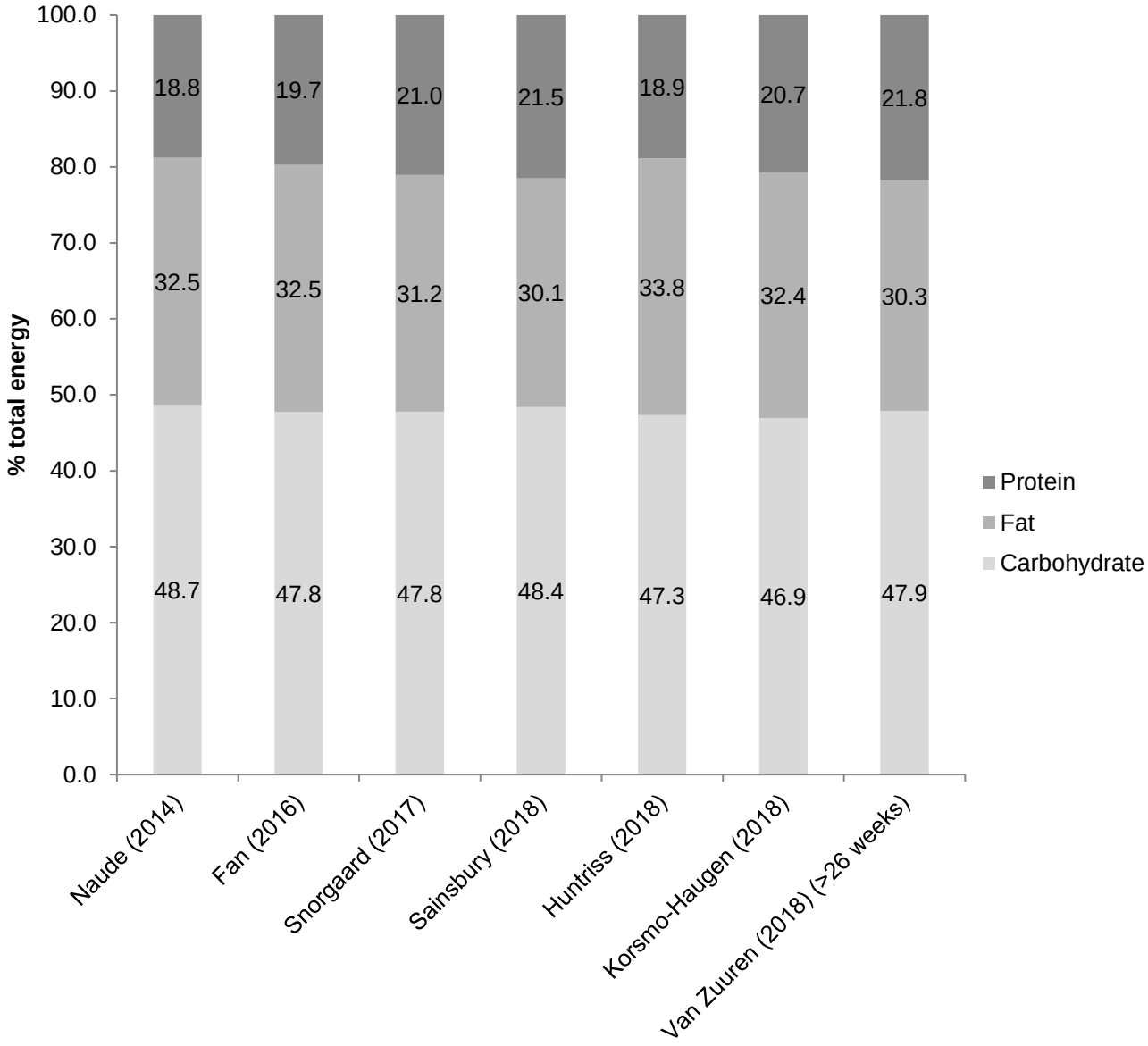
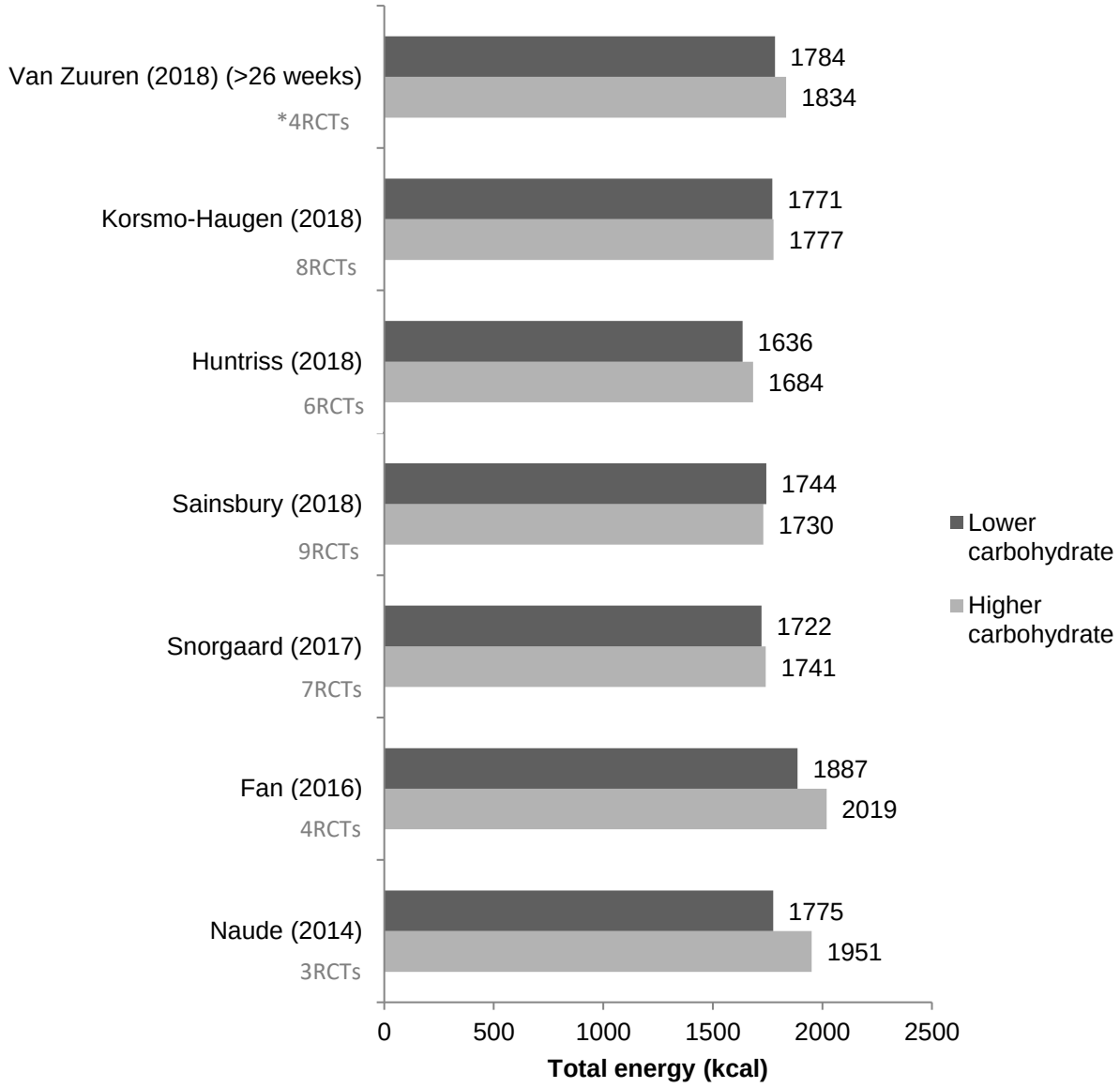
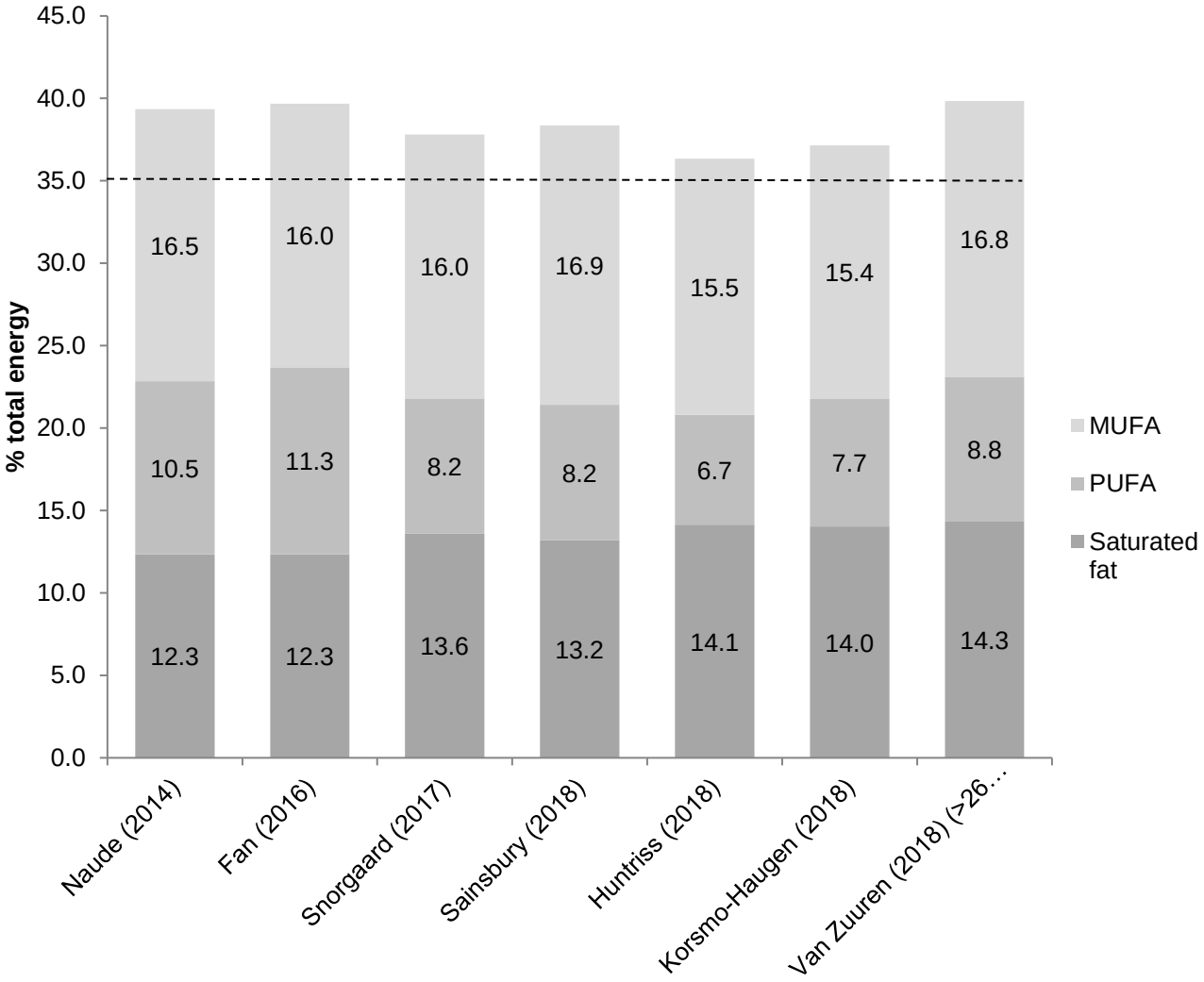


Figure A8.7: Average reported energy intakes (kcal/d) in lower and higher carbohydrate groups



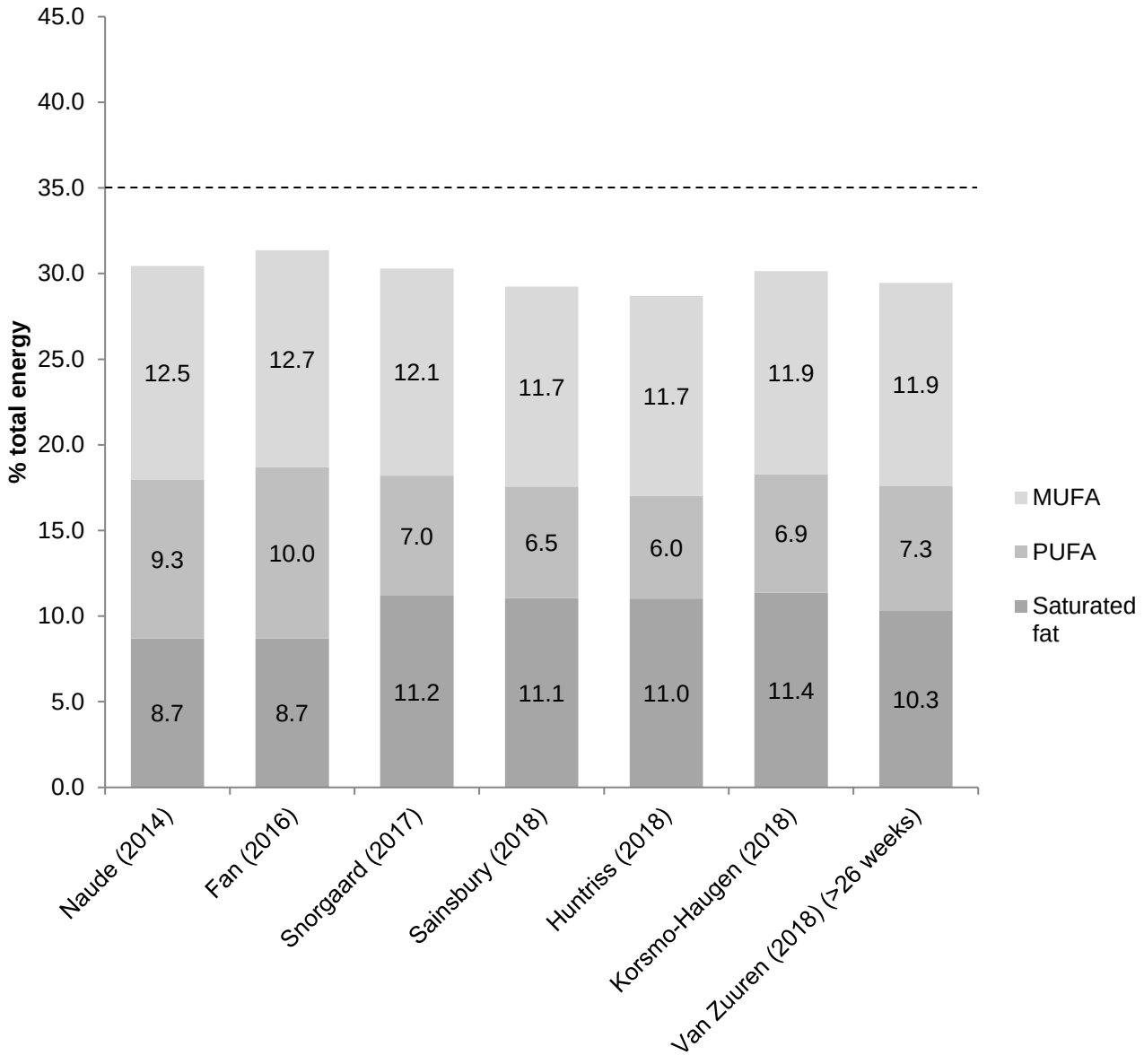
*Indicates number of RCTs the average energy intakes are based on (not all RCTs included in the meta-analyses reported energy intakes).

Figure A8.8: Average reported fat intakes in lower carbohydrate groups



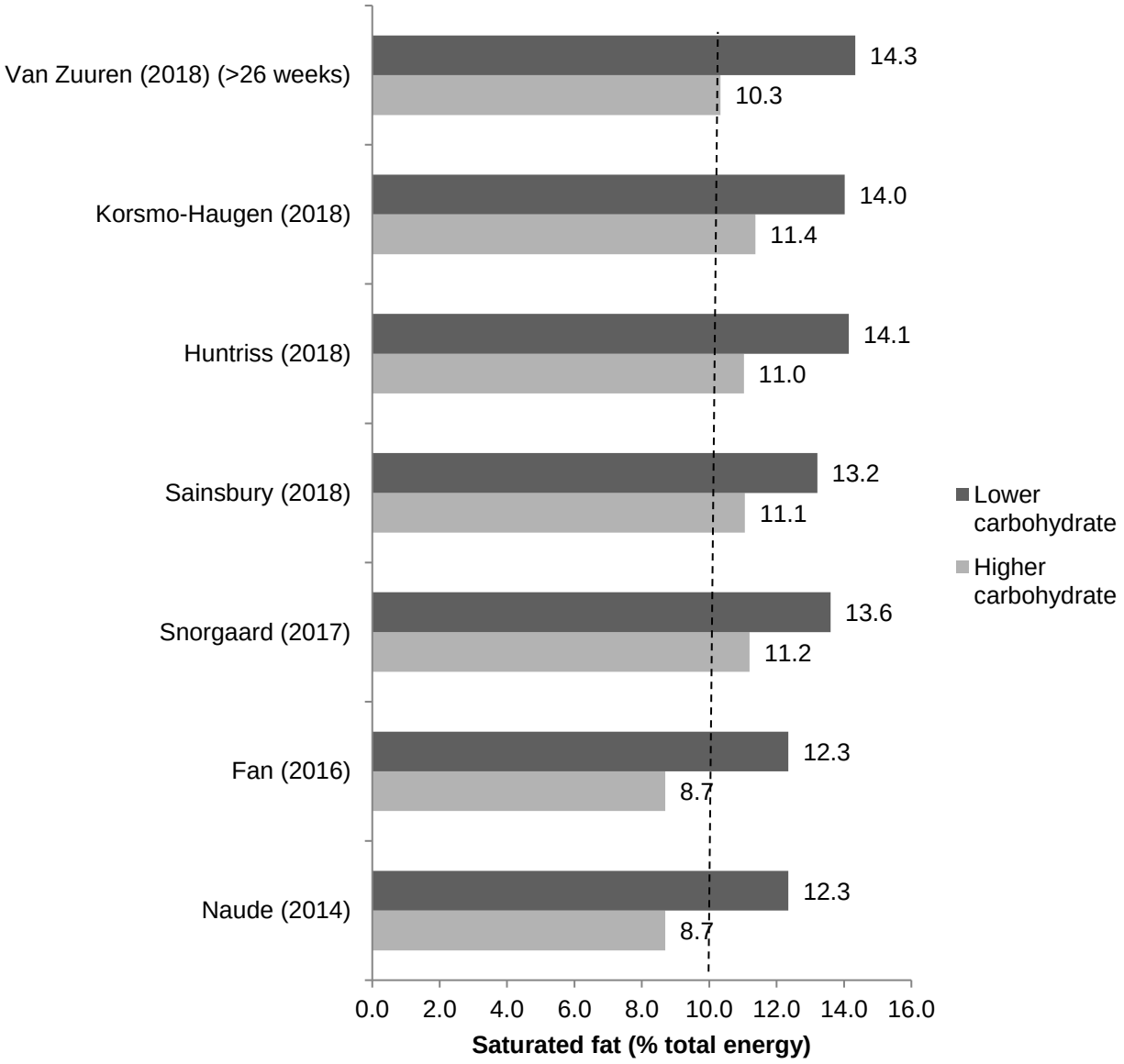
Recommendations: saturated fats, no more than 10% of total dietary energy; PUFA, not exceeding 10% of total dietary energy; MUFA, around 12% of total dietary energy. The horizontal dashed line (---) represents the DRV for total fat (35% total dietary energy) (DH, 1994).

Figure A8.9: Average reported fat intakes in higher carbohydrate groups



Recommendations: saturated fats, no more than 10% of total dietary energy; PUFA, not exceeding 10% of total dietary energy; MUFA, around 12% of total dietary energy. The horizontal dashed line (---) represents the DRV for total fat (35% total dietary energy) (DH, 1994).

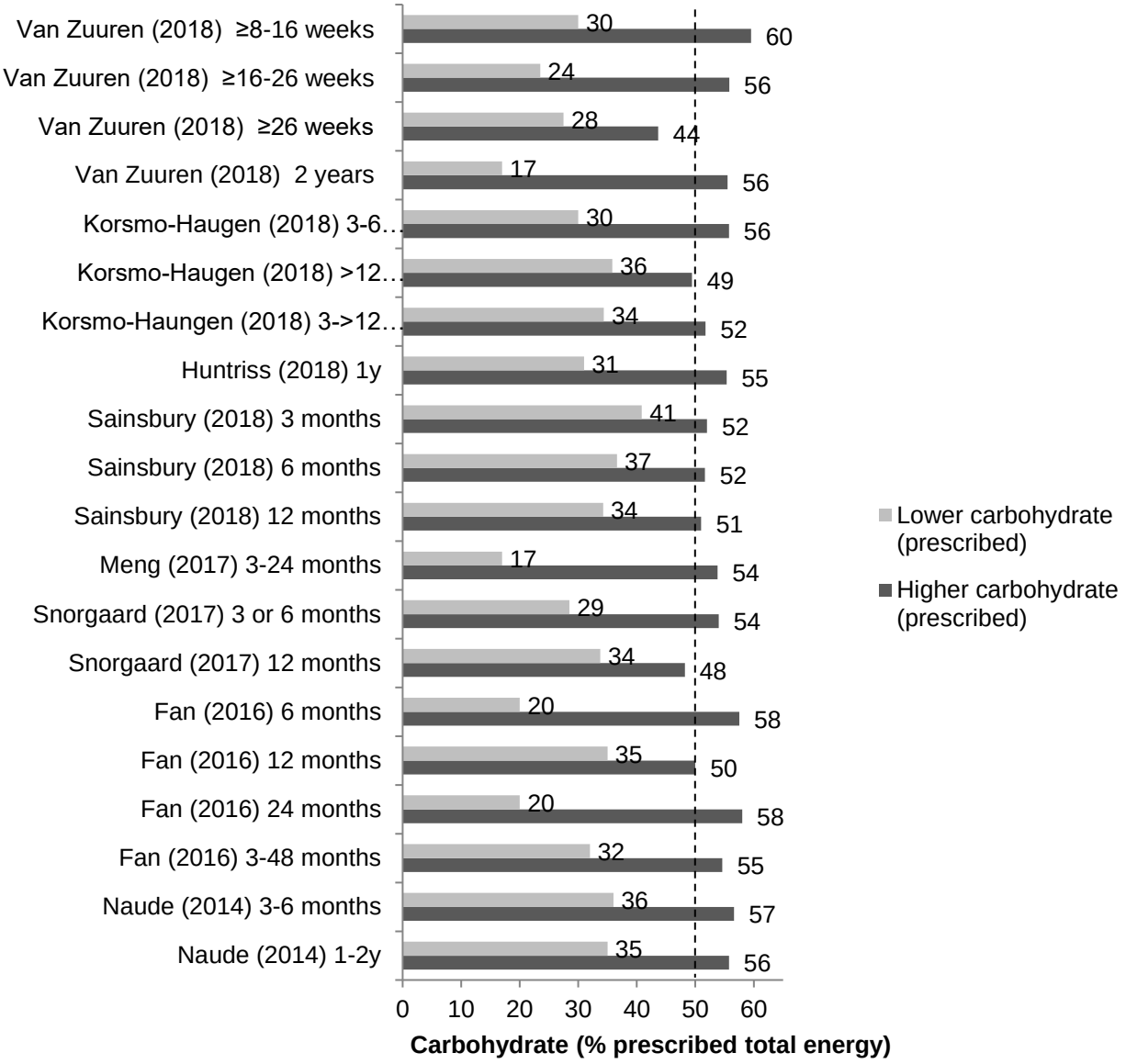
Figure A8.10: Average reported intakes of saturated fats in lower and higher carbohydrate groups



The vertical dashed line (---) represents the DRV for saturated fats (no more than 10% of total dietary energy).

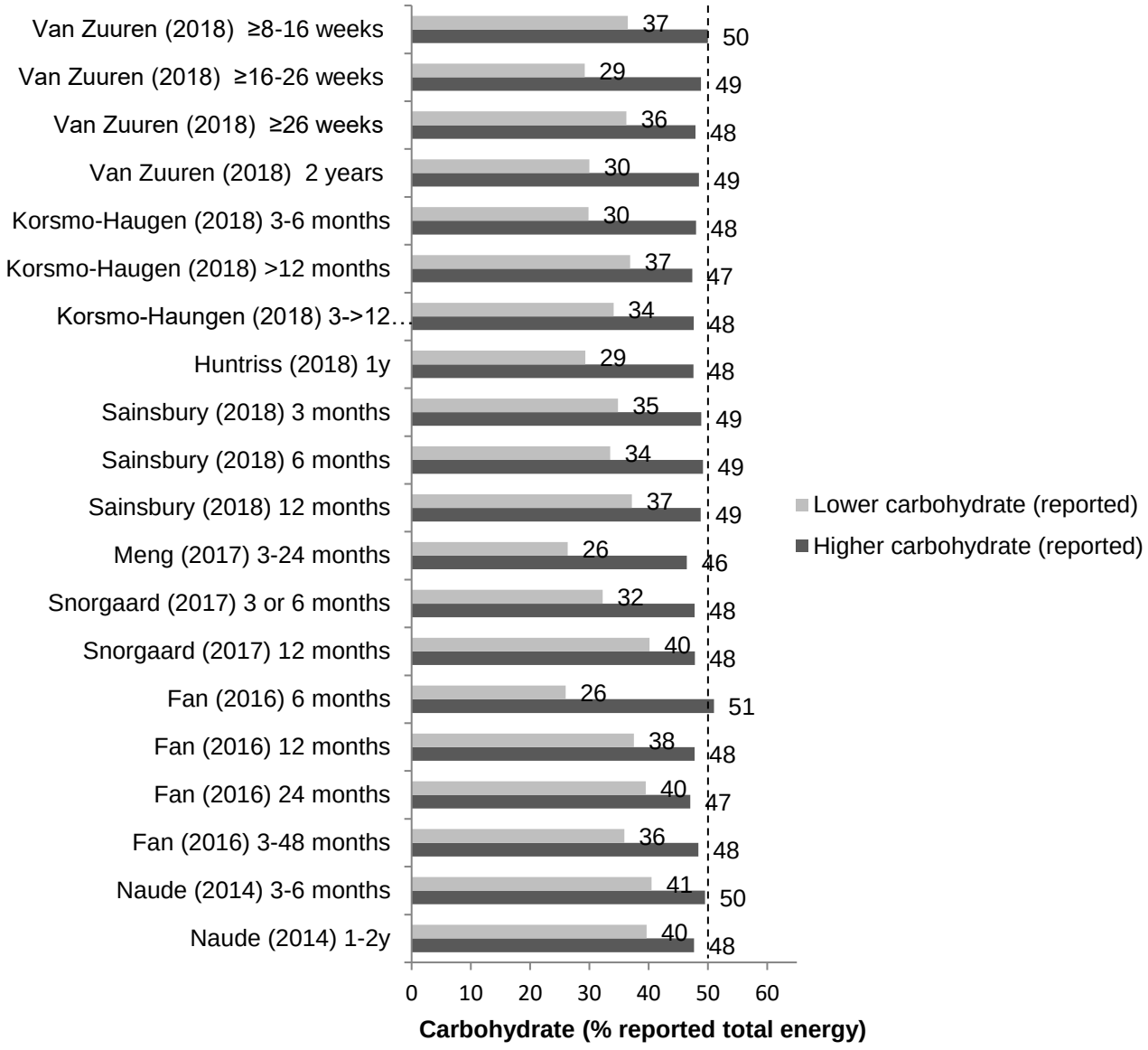
Data presented from meta-analyses for the outcome of HbA1c (Figures A8.11 to A8.20)

Figure A8.11: Average prescribed intakes of carbohydrate in lower and higher carbohydrate groups (% of total prescribed energy)



The vertical dashed line (---) represents the DRV for total carbohydrate (approximately 50% of total dietary energy) (SACN, 2015).

Figure A8.12: Average reported intakes of carbohydrate in lower and higher carbohydrate groups



The vertical dashed line (---) represents the DRV for total carbohydrate (approximately 50% of total dietary energy) (SACN, 2015).

Figure A8.13: Difference in average prescribed carbohydrate intakes in lower and higher carbohydrate groups versus difference in average reported carbohydrate intakes in lower and higher carbohydrate groups

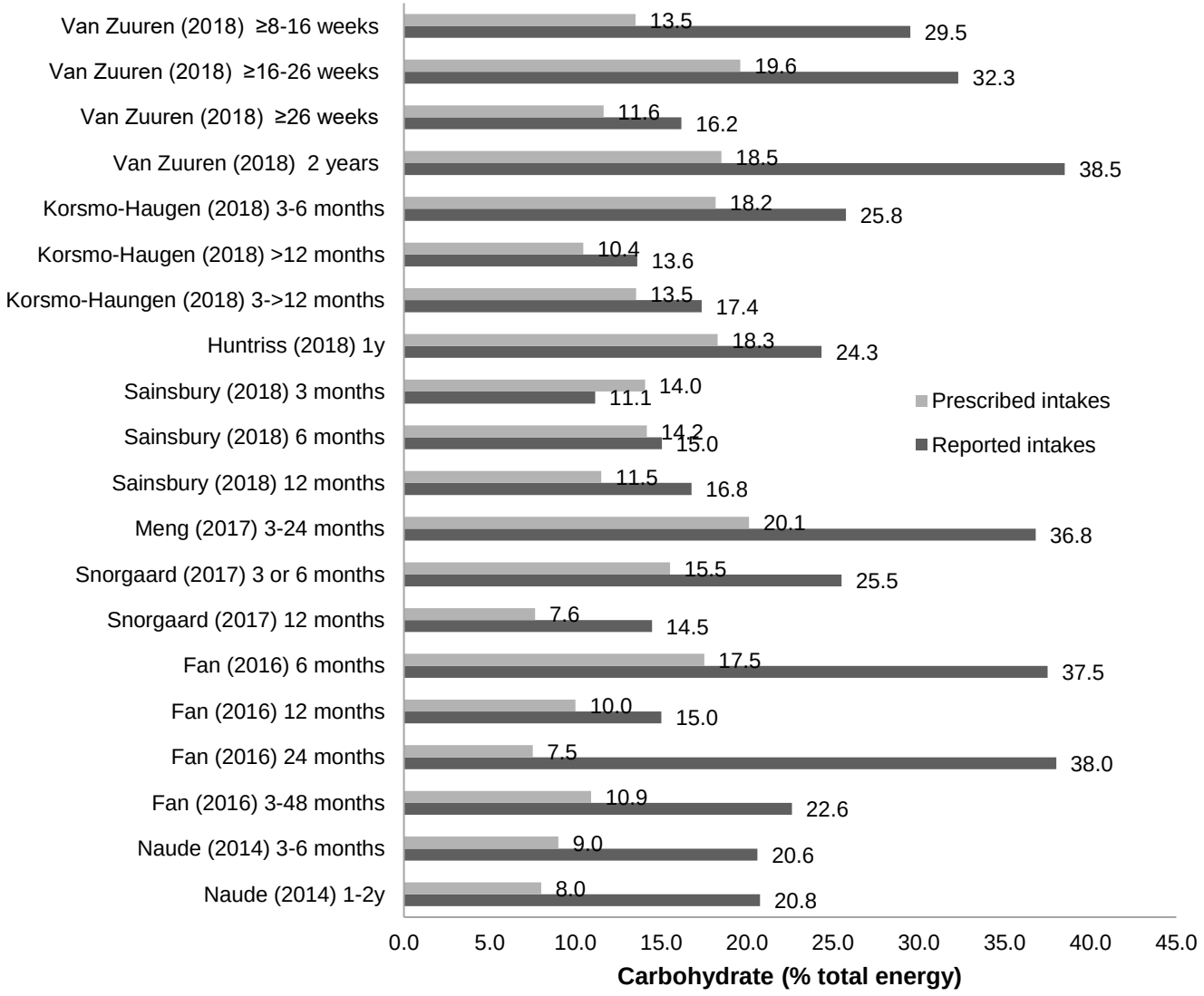
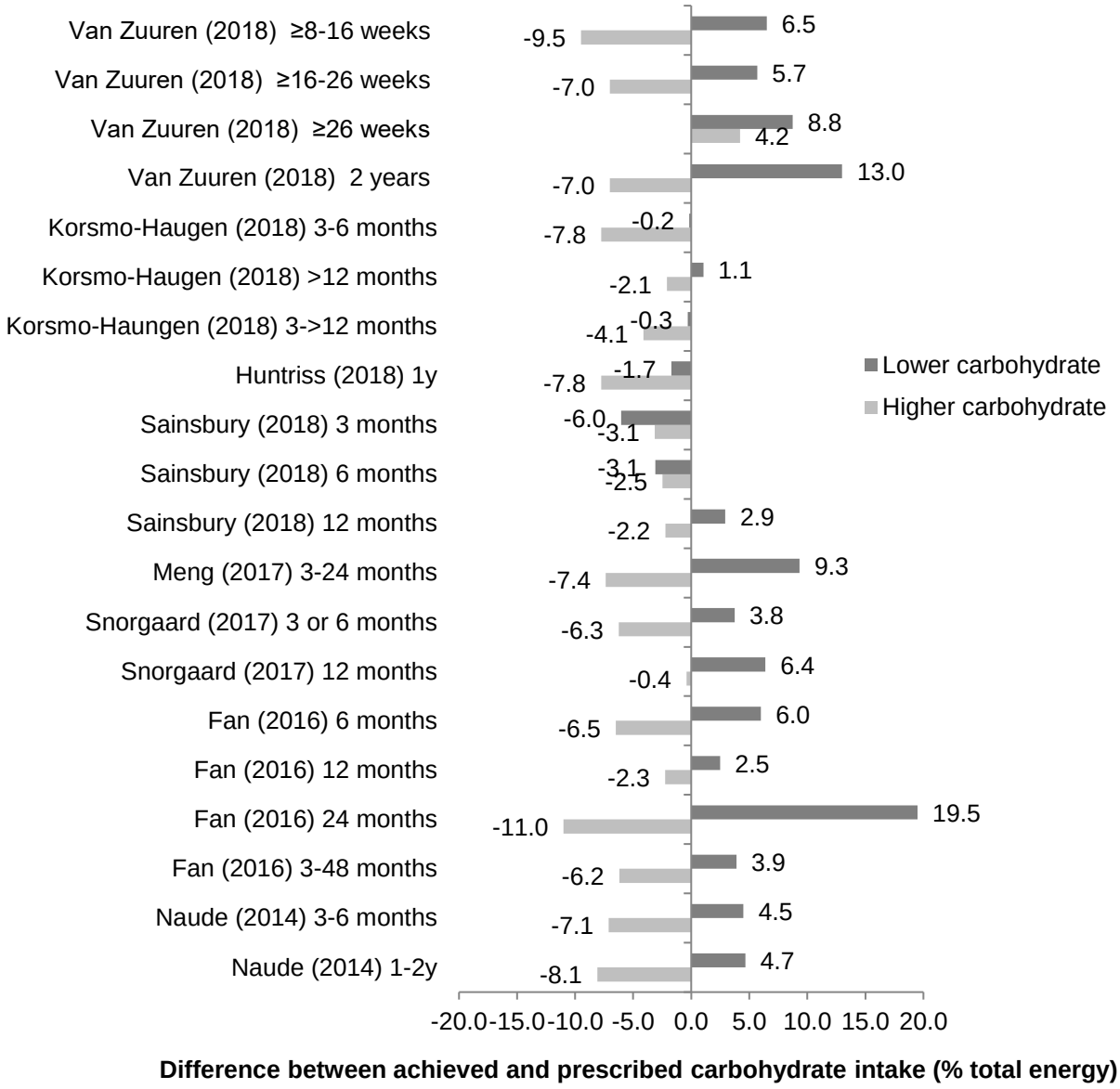


Figure A8.14: Adherence to the average prescribed intakes of carbohydrate in the lower and higher carbohydrate groups



Positive and negative values indicate that the average reported intake was above or below the prescribed intake, respectively.

Figure A8.15: Average reported intakes of carbohydrate, fat and protein in lower carbohydrate groups

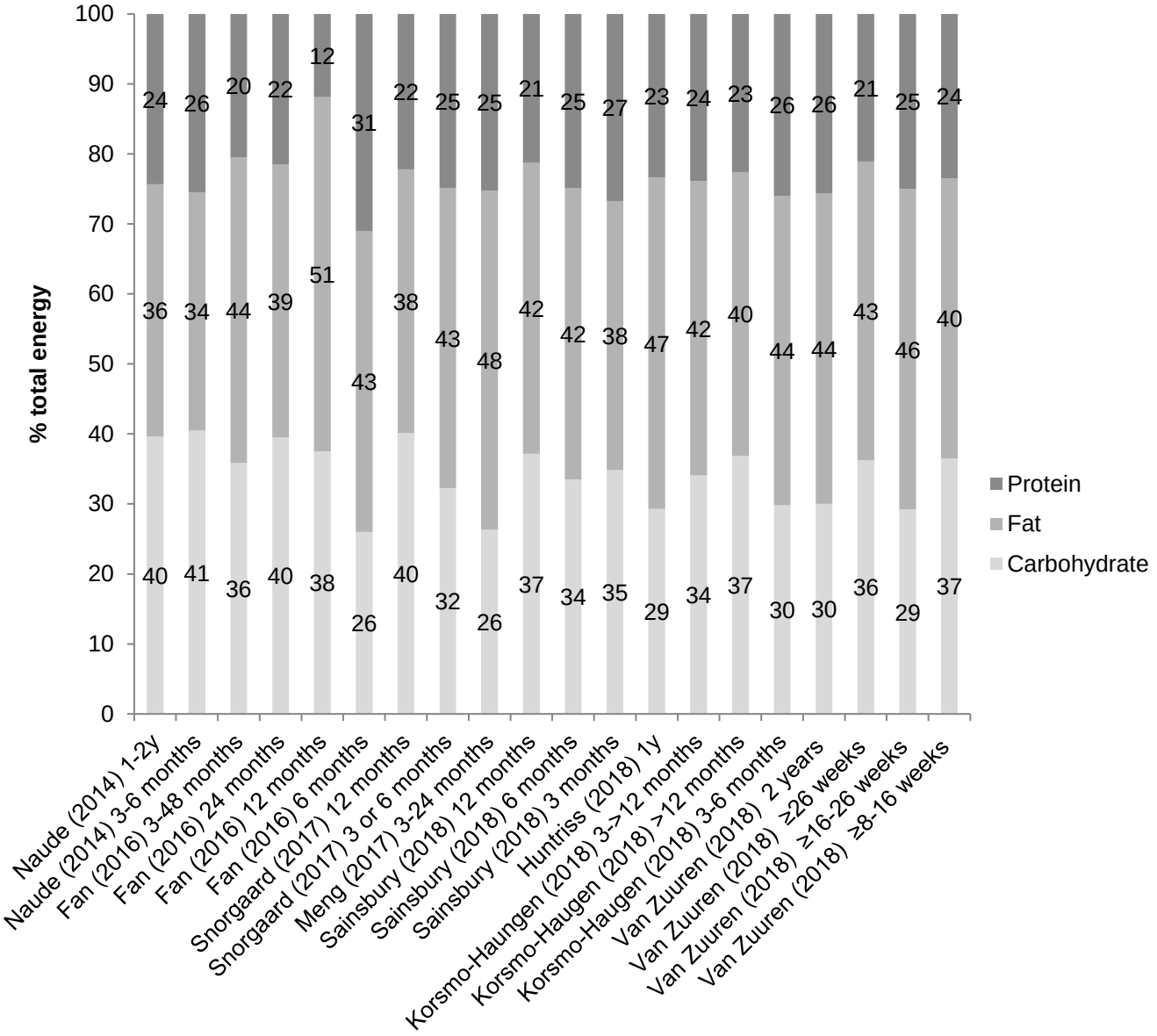


Figure A8.16: Average reported intakes of carbohydrate, fat and protein in higher carbohydrate groups

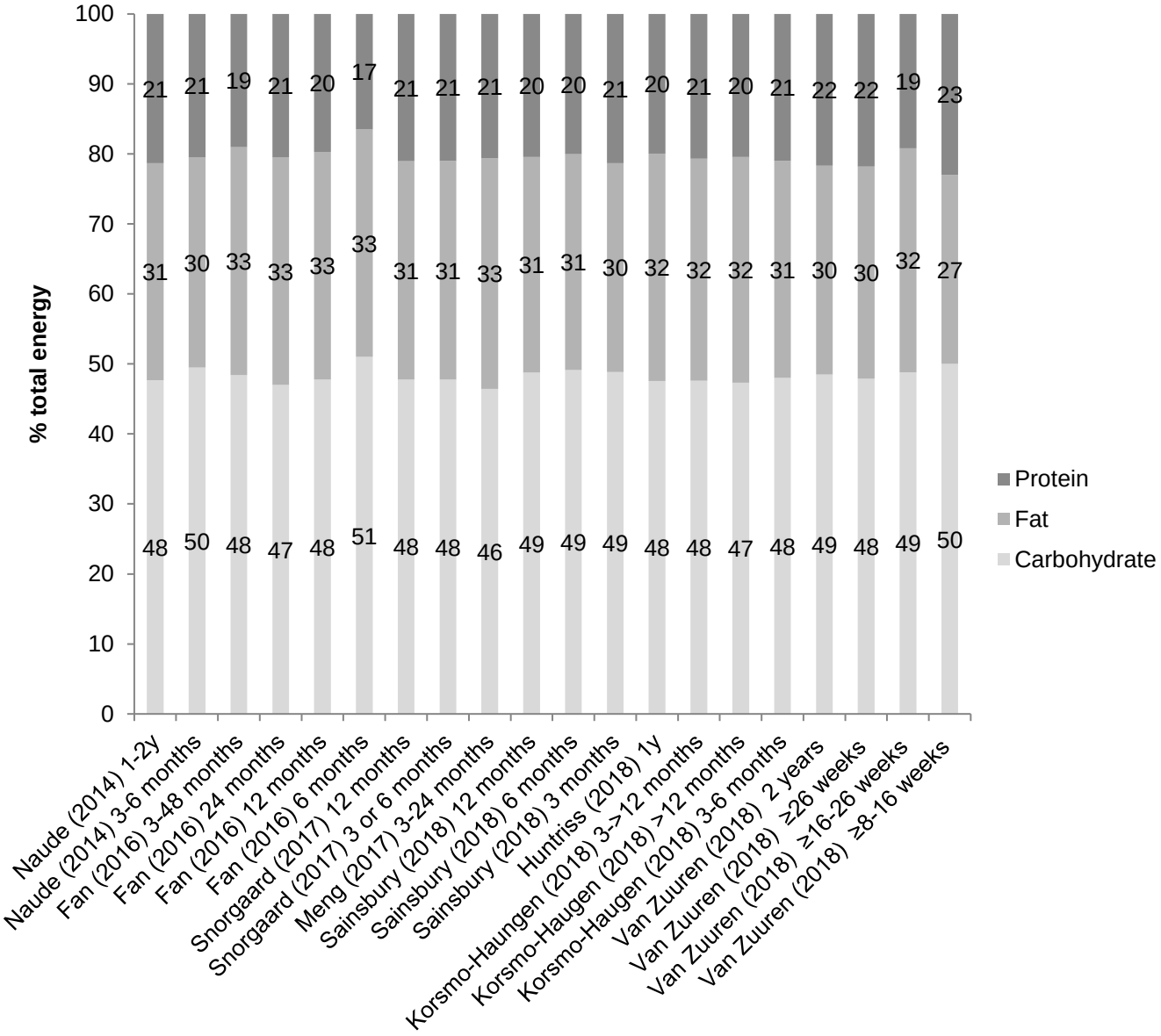
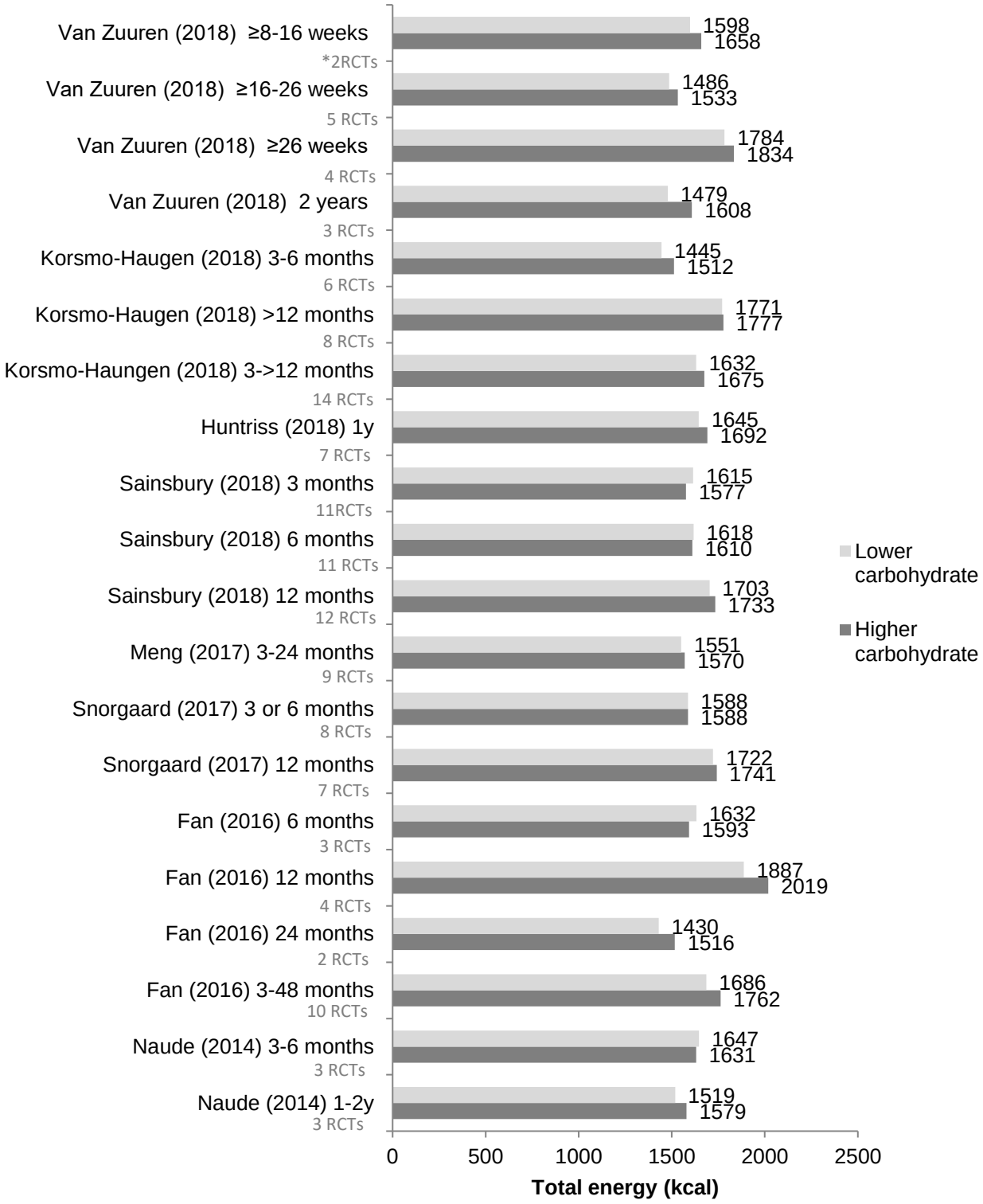
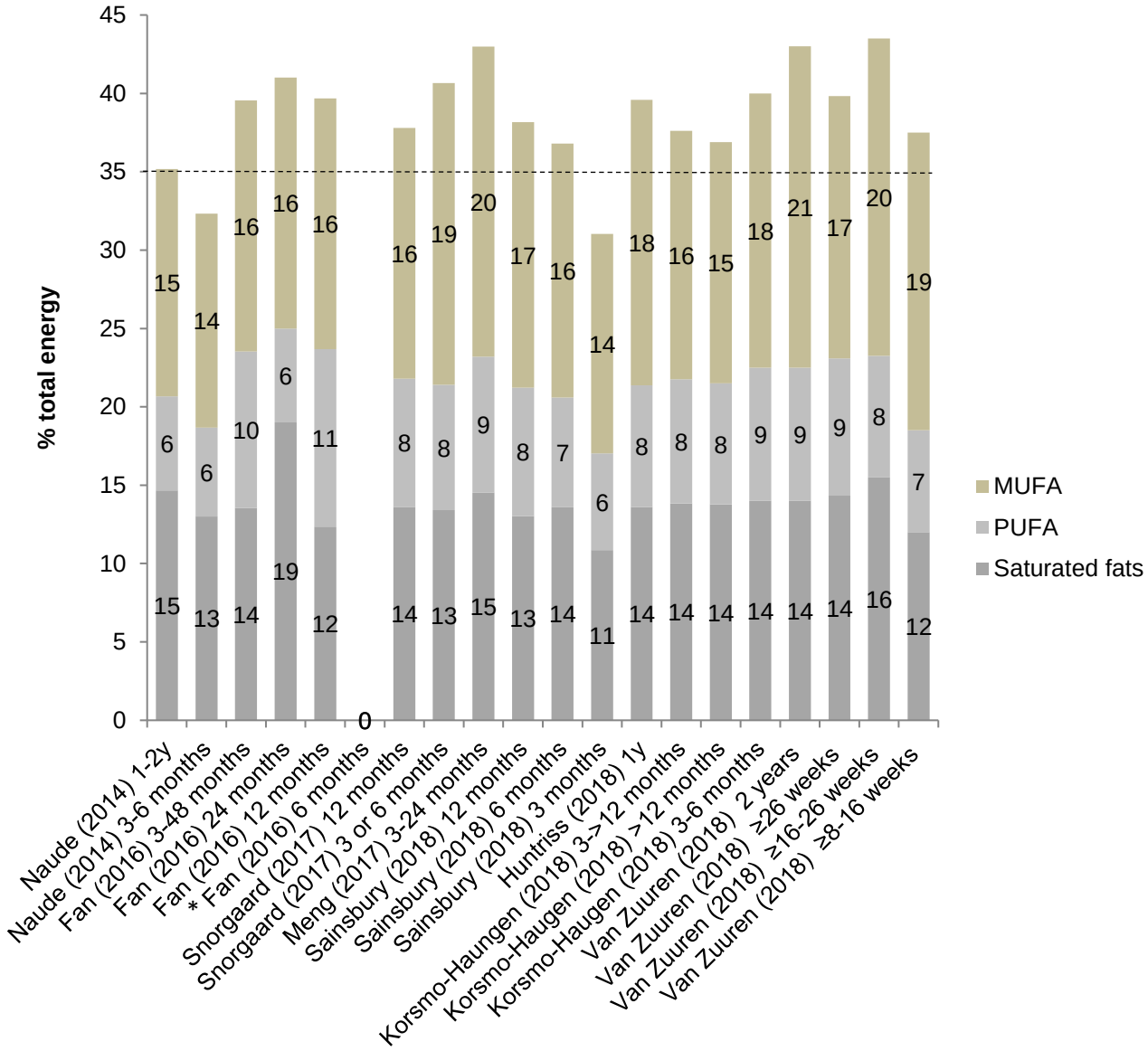


Figure A8.17: Average reported energy intakes (kcal/d) in lower and higher carbohydrate groups



*Indicates the number of RCTs the average energy intakes are based on (not all RCTs included in the meta-analyses reported energy intakes).

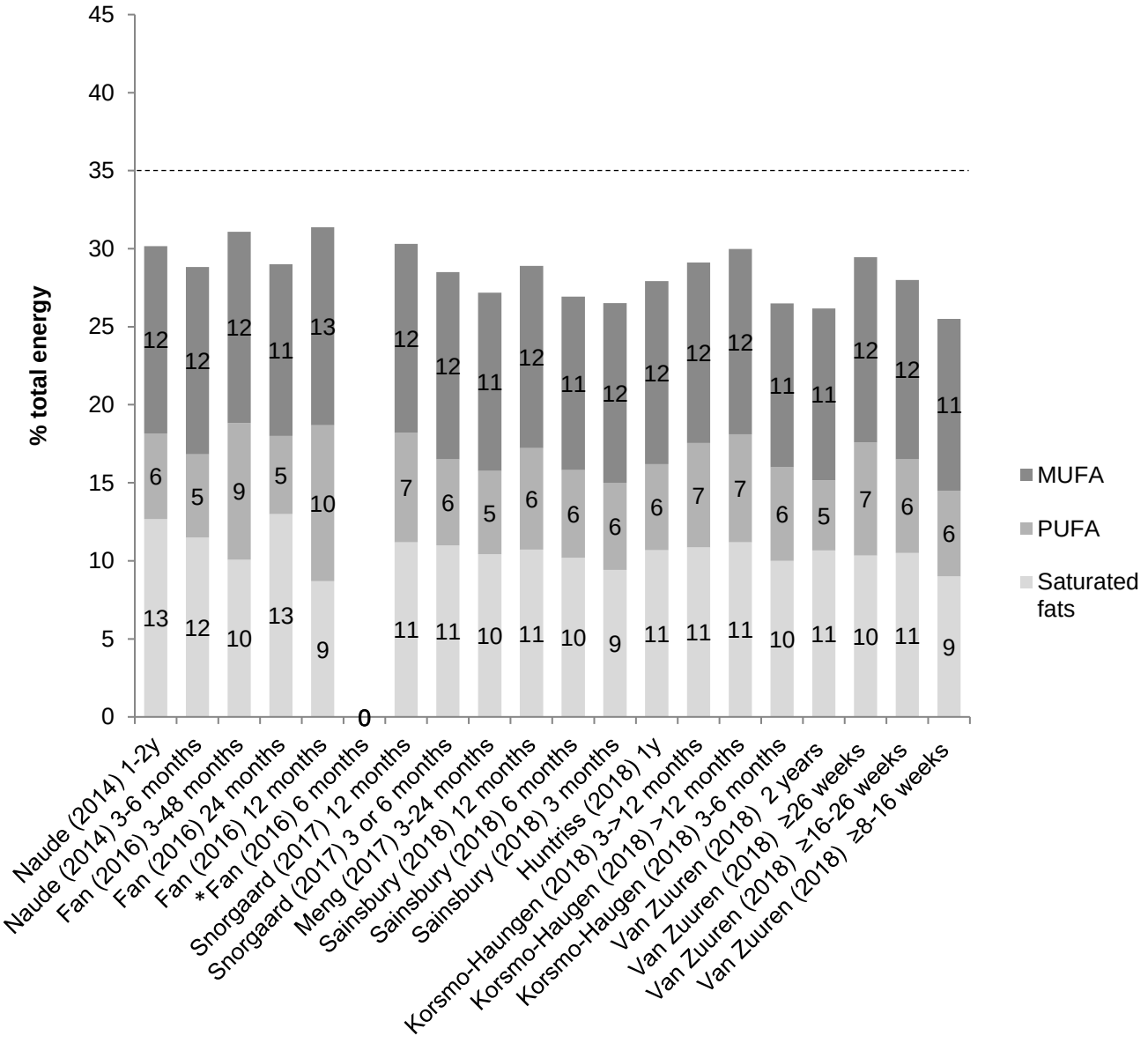
Figure A8.18: Average reported fat intakes in lower carbohydrate groups



*Fan et al (2016) 6 months did not include primary studies that reported intakes of fatty acids.

Recommendations: saturated fats, no more than 10% of total dietary energy; PUFA, not exceeding 10% of total dietary energy; MUFA, around 12% of total dietary energy. The horizontal dashed line (---) represents the DRV for total fat (35% total dietary energy) (DH, 1994).

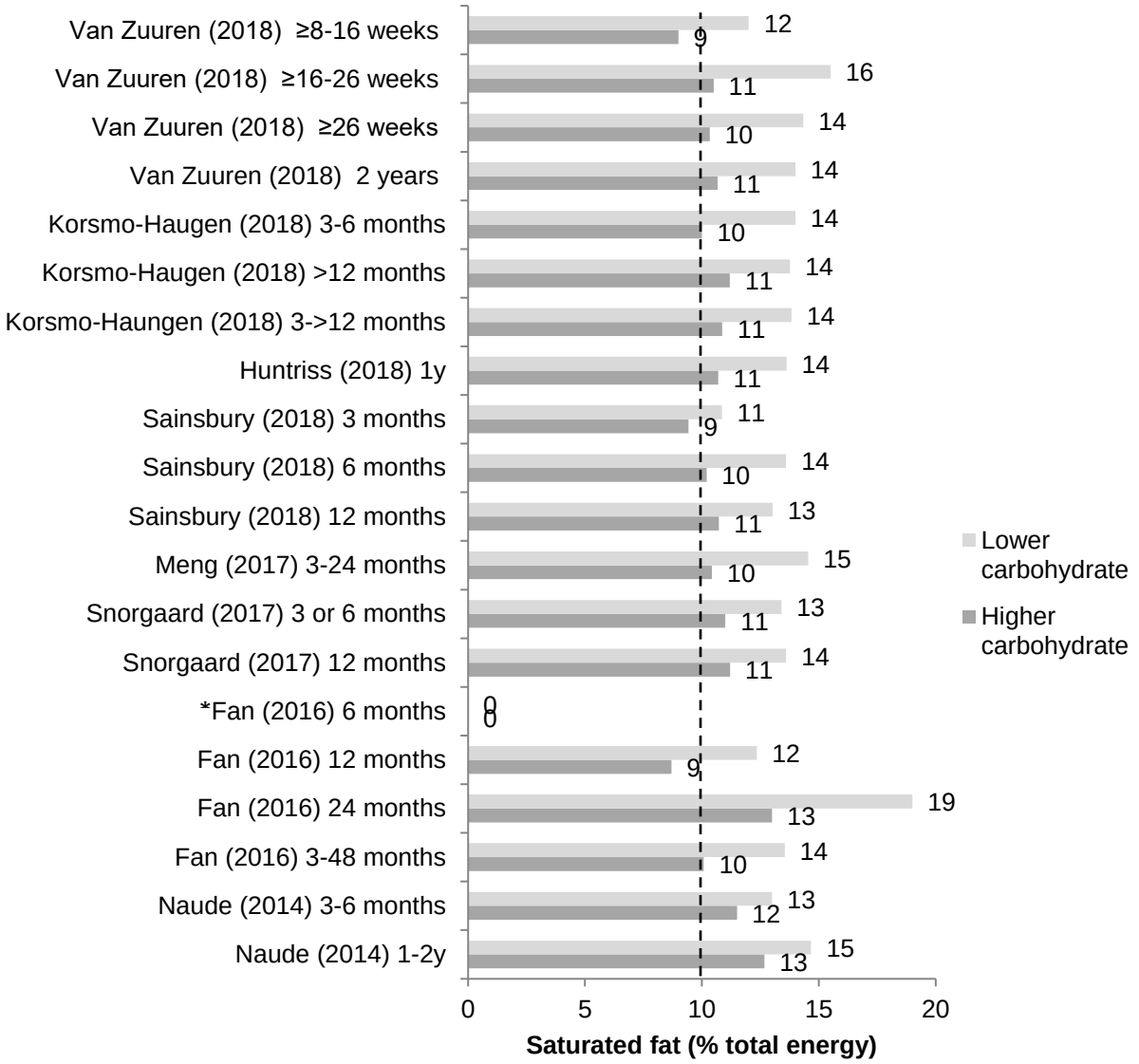
Figure A8.19: Average reported fat intakes in higher carbohydrate groups



*Fan et al (2016) 6 months did not include primary studies that reported intakes of saturated fats.

Recommendations: saturated fats, no more than 10% of total dietary energy; PUFA, not exceeding 10% of total dietary energy; MUFA, around 12% of total dietary energy. The horizontal dashed line (---) represents the DRV for total fat (35% total dietary energy) (DH, 1994).

Figure A8.20: Average reported intakes of saturated fats in lower and higher carbohydrate groups



*Fan et al (2016) 6 months: did not include primary studies that reported intakes of saturated fats.

The vertical dashed line (---) represents the DRV for saturated fats (10% of total dietary energy).

Annex 9: AMSTAR 2 assessment of the 8 eligible systematic reviews with meta-analyses

Table A9.1: Summary of results

Domains		van Zuuren (2018)	Korsmo Haugen (2018)	Sainsbury (2018)	Huntriss (2018)	Snorgaard (2017)	Meng (2017)	Fan (2016)	Naude (2014)
Domains 2, 4, 7, 9, 11, 13, 15 are considered critical by AMSTAR 2; in addition, domain 8 was considered to be critical in this assessment									
1	Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, control group, outcome)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Yes	Yes	Yes	No	No	No
3	Did the review authors explain their selection of the study designs for inclusion in the review? (To note: considered this was not applicable since RCTs are preferable to other type of study designs.)	NA	NA	NA	NA	NA	NA	NA	NA
4	Did the review authors use a comprehensive literature search strategy? Marked as 'yes' if met the following: searched 2 databases; provided key word and/or search strategy; searched reference lists of included studies; searched trial/study registries/conducted search within 24 months of completion of the review.	Yes	Partial yes	Yes	Yes	Partial yes	No	No	Yes
5	Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
6	Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	No	No	No	No	No	Yes

Domains		van Zuuren (2018)	Korsmo Haugen (2018)	Sainsbury (2018)	Huntriss (2018)	Snorgaard (2017)	Meng (2017)	Fan (2016)	Naude (2014)
8	Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	No	Yes	No	No	Yes
9	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	No	No	Yes
10	Did the review authors report on the sources of funding for the studies included in the review?	Yes	No	Yes	No	No	No	No	Yes
11	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Assumed adjusted for heterogeneity if random-effects model was used.)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
12	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes	No	Yes	Yes	No	Yes
13	Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes	Yes	Yes	No	Yes	Yes	No	Yes
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	No	No
15	If they performed quantitative synthesis (1) did the review authors carry out an adequate investigation of publication bias (small study bias) and (2) discuss its likely impact on the results of the review?	Too few studies identified	Yes	No	No	No	Yes	Too few studies identified	No
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Annex 10: Overview and limitations of the 4 non-prioritised systematic reviews with meta-analyses and 1 network meta-analysis

The results from 4 SRs with MAs (Meng et al, 2017; Snorgaard et al, 2017; Fan et al, 2016, Naude et al, 2014) and 1 NMA (Schwingshackl et al, 2018) were not considered when grading the evidence. An overview of these publications and their limitations are briefly summarised below.

Meng et al (2017) (9 RCTs; 734 participants): evaluated the effect of a low carbohydrate diet (26% TE) with a normal or high carbohydrate diet (not defined). The primary outcome was weight change; secondary outcomes were fasting plasma glucose, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol. MAs were performed for change in each of these outcomes. No subgroup or sensitivity analyses were conducted.

Limitations: most of the primary studies were of shorter duration; in the MA for weight change only 3 out of the 9 RCTs (n=734) were ≥12 months duration. Although a subgroup analysis was carried out for studies ≥12 vs <12 months duration, 1 of the RCTs in the ≥12 months subgroup had a duration of 24 weeks. Insufficient detail was provided in the risk of bias analysis. Only 1 primary study included in this SR with MA was not included in more recent 4 SRs with MAs.

Snorgaard et al (2017) (10 RCTs; 1376 participants): compared diets containing low to moderate amounts of carbohydrates (<45% TE) to diets containing high amounts of carbohydrate (45 to 60% TE). Primary outcomes were HbA1c and BMI after 1 year; secondary outcomes were HbA1c and BMI before 1 year, LDL cholesterol, quality of life (QoL) and drop-out rates. MAs were performed for change in each of these outcomes (except QoL). No subgroup or sensitivity analyses were conducted.

Limitations: no information was provided on statistical analysis; although 7 studies were ≥12 months duration, only 6 were included in the MA for weight change and were not specified. It was also not clear if the results were differences between groups in weight change or in actual weight at study end. In the MA for HbA1c, difference between groups in HbA1c change were mixed with differences in actual HbA1c. Only 1 primary study included in this SR with MA was not included in more recent 4 SRs with MAs.

Fan et al (2016) (10 RCTs; 1080 participants): evaluated the effect of low carbohydrate diets (26% TE) on the following outcomes: weight, HbA1c, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol. The authors did not distinguish between primary and secondary outcomes. Subgroup analysis was performed to explore the effect of study duration on change in weight and HbA1c. A sensitivity analysis was performed to identify potential sources of heterogeneity.

Limitations: results were not clearly presented and were not the same in the text (weighted mean difference) and forest plots (standard mean difference). One RCT was included twice in the MA because it had 3 intervention arms (resulting in double-counting of participants in the lower carbohydrate group). Only 2 primary studies included in this SR with MA were not included in more recent 4 SRs with MAs.

Naude et al (2014) (5 RCTs, 720 participants): compared the effects of low carbohydrate diets [<45% TE; 2 variants: high fat variant (carbohydrate <45% TE, fat >35% TE, protein >20% TE) or high protein variant (carbohydrate <45% TE, fat 25 to 35% TE, protein >20% TE)] with isoenergetic balanced weight loss diets on the following outcomes: weight, HbA1c, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol. The authors did not distinguish between primary and secondary outcomes. MAs were performed for all outcomes. Subgroup analysis was performed to explore effect of the high fat or high protein variant of the lower carbohydrate diets.

Limitations: included a small number of studies (4 RCTs, 492 participants) which were all covered in the more recent MAs. In the MA of weight change, differences between groups in weight change were mixed with differences in actual weight at study end.

Schwingshackl et al (2018) (56 RCTs, 4397 participants): compared the efficacy of 9 different dietary approaches on HbA1c (primary outcome) and fasting blood glucose (FBG) (secondary outcome). Only the comparisons relating to low carbohydrate (defined as <25% TE) and moderate carbohydrate (defined as 25 to 40% TE) interventions were considered. A low carbohydrate diet was compared with a control diet (no or minimal intervention) (all indirect comparisons), a moderate carbohydrate diet (77% indirect comparisons), a low-fat diet (defined as <30% TE) (17% indirect comparisons), or a high protein diet (defined as >20% TE) (all indirect comparisons). A moderate carbohydrate diet was compared to a control diet (81% indirect comparisons), a low-fat diet (43% indirect comparisons) and a high protein diet (all indirect comparisons). NMA was performed for both outcomes; subgroup analysis explored the effect of study duration (≥12 versus <12 m), sample size (≥100 versus <100) and age (≥60 versus <60 y). Sensitivity analyses were conducted for studies considered to be at low risk of bias.

Limitations: the NMA 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. The authors highlighted significant inconsistency for HbA1c in the comparisons and rated the credibility of the evidence as very low for comparisons between low carbohydrate vs low fat diets, low carbohydrates vs high protein diets and moderate vs low carbohydrate diets. They suggest that the inconsistency might reflect the low contribution of direct comparisons to the total estimate.

Annex 11: Main changes to draft report following public consultation

Previous Draft (January 2020)	**Revised draft** (September 2020)
Chapter 1 – Introduction	• Added new paragraph explaining that since there is no agreed definition of a 'low' carbohydrate diet, comparisons were between lower and higher carbohydrate intakes. • Added sentence to clarify that the evidence considered in the SACN review on carbohydrates (2015) comprised studies in the general population and recommendations were made for the UK general population.
Chapter 2 – Background previously • Chapter 2 – Background on carbohydrates • Chapter 3 – background on T2D	Merged chapters 2 and 3 into one background chapter with 3 sections: carbohydrates; T2D; evidence from clinical practice. <u>Section on T2D</u> • Added new paragraph on T2D risk in minority ethnic population groups. <u>Section on evidence from clinical practice</u> • Added new section on evidence from clinical practice (previously in Methods chapter) • Expanded text to include more information on these types of studies including direction of the evidence and a more detailed explanation of why they were not considered in report.
Chapter 3 – Markers and clinical outcomes of T2D (previously chapter 4)	• Added new paragraph explaining that shorter-term weight loss (≥3 to <12 months) would be considered as a secondary outcome • The secondary outcome 'medication use and diabetes related symptoms' was changed to 'medication use'.

Chapter 4 – Methods (previously chapter 5)	• Moved paragraphs on evidence from clinical practice to the background chapter • Changes made to clarify the sections on literature search, study selection and data extraction • Edited flow diagram of study selection process to align more clearly with text • Moved paragraphs that were originally at the beginning of the evidence review chapter (explaining evidence prioritisation process) into this chapter and included additional flow diagram summarising how evidence was prioritised.
Chapter 5 – Assessment of the evidence (previously chapter 6)	• Changed 'achieved' carbohydrate intakes to 'reported' carbohydrate intakes • Added results of medication use in primary RCTs • Added evidence grading for shorter-term (≥3 to <12 months) weight loss and for medication use • Edited section on potential adverse events.
Chapter 6 – overall summary and conclusions (previously chapter 7)	• Editing changes to make chapter more concise • Added summary of characteristics of primary studies • Replaced narrative description of macronutrient and energy intakes with table • Added paragraph about diabetes medication use.

Annex 12: Primary and secondary outcomes considered in prioritised systematic reviews with meta-analyses

Table A12.1: Markers and clinical outcomes of T2D considered in prioritised systematic reviews with meta-analyses

First author (year)	Body weight	HbA1c	Fasting plasma glucose	Serum triacylglycerol	Serum total cholesterol	Serum HDL cholesterol	Serum LDL cholesterol	Total cholesterol: HDL cholesterol ratio	Medication use
van Zuuren et al (2018)	✓	✓	✓	✓	x	✓	✓	x	x
Korsmo-Haugen et al (2018)	✓	✓	x	✓	✓	✓	✓	x	x
Sainsbury et al (2018)	✓	✓	x	Qualitative evaluation				x	x
Huntriss et al (2018)	✓	✓	x	✓	✓	✓	✓	x	✓
Total number SR/MAs that considered outcome	4	4	1	3	2	3	3	0	1

Annex 13: Risk of bias analysis for prioritised systematic reviews with meta-analyses

- Risk of bias (RoB) analysis for each of the 4 prioritised SRs with MAs is summarised in Table A13.1 below.
- All used the Cochrane RoB tool to assess the quality of RCTs.
- Korsmo-Haugen et al (2018) and van Zuuren et al (2018) specified the criteria for overall RoB (low, high, unclear) but the criteria differed across these 2 SRs. Sainsbury et al (2018) did not state criteria explicitly but referred to the Cochrane handbook (and this wording is included in Table A13.1).
- van Zuuren et al (2018) included 3 non-randomised controlled trials and used a different assessment tool (ROBINS-I) to assess the quality of these studies.
- The RoB assessment for all the primary RCTs included in the MAs of 3 SRs (Korsmo-Haugen et al, 2018; Sainsbury et al, 2018; van Zuuren et al, 2018) is provided in Table A11.2. One SR (Huntriss et al, 2018) did not report overall RoB for each RCT separately.
- There was disagreement between SRs in the overall RoB for 8 RCTs (shaded grey in Table A13.2).

Table A13.1: RoB reported in the 4 prioritised systematic reviews

Systematic review (lead author, year)			
Huntriss et al (2018)	**Korsmo-Haugen et al (2018)**	**Sainsbury et al (2018)**	**van Zuuren et al (2018)**
Domains for assessment 1. Random sequence generation 2. Allocation concealment 3. Blinding of participants and personnel 4. Blinding of outcome assessment 5. Incomplete outcome data 6. Selective reporting **Overall RoB criteria** Not reported	**Domains for assessment** 1. Random sequence generation 2. Allocation concealment 3. Blinding of participants and personnel 4. Blinding of outcome assessment 5. Incomplete outcome data 6. Selective reporting 7. Other sources of bias **Overall RoB criteria** Low risk: No high RoB and not more than 2 unclear RoB	**Domains for assessment** 1. Selection bias 2. Performance bias 3. Detection bias 4. Reporting bias 5. Attrition bias **Overall RoB criteria** Criteria for low risk, high risk and unclear risk per the Cochrane Handbook for Systematic Reviews of Interventions was used (2011). **RoB of included studies** 15 studies reported using random sequence generation; remaining	**Domains for assessment** RoB for each RCT assessed with the use of the Cochrane Collaboration's domain-based assessment tool. **Overall RoB criteria** Low risk: All domains assessed as low risk (plausible bias unlikely to seriously alter results). High risk: ≥1 domain judged as being at high risk (plausible bias that seriously weakens confidence in results). Unclear risk: ≥1 domain classified as an unclear

Systematic review (lead author, year)			
Huntriss et al (2018)	**Korsmo-Haugen et al (2018)**	**Sainsbury et al (2018)**	**van Zuuren et al (2018)**
RoB of included studies: • 15 out of 18 studies (83%) considered at high risk of performance bias (due to nature of intervention, authors had difficulty in blinding participants and study personnel). • Some studies at risk of detection bias (lack of blinding of those assessing nutritional composition of diets). • Insufficient detail of study processes often resulted in the categorisation of unclear RoB. **Overall study level assessment** • Not reported **Comment:** Review authors did not specify which domains they considered key or critical to the overall study level assessment.	High risk: 2 or more high RoB, 1 high and more than one unclear risk, or more than 4 unclear RoB Unclear risk: remaining articles classified as unclear RoB **RoB of included studies**: • Method of random sequence generation reported and found to be adequate in 15 trials. • 8 trials provided sufficient information on allocation concealment and were rated as low risk. • Few studies blinded study participants and personnel to dietary interventions (except 1) and were rated as unclear risk. • 5 trials reported blinding of outcome assessors. • 1 trial at high risk of attrition bias, incomplete reporting of outcome data as only compliers included in analysis. • Selective reporting in 4 trials. **Overall study level assessment** • High: 10 • Low: 3 • Unclear: 10	studies did not provide sufficient information. • Allocation concealment poorly reported across majority of studies (n=22). • Due to inherent difficulties in blinding participants and personnel, it was assumed, unless otherwise stated, that no blinding was conducted. Consequently, RoB high across all studies for self-reported outcomes due to possible bias in participants self-reported dietary intake and analysis of food records. • Other biases: 8 studies classified as high or unclear RoB due to stated conflicts of interest from funding sources. **Overall study level assessment** • High: 7 • Low: 9 • Unclear: 9 **Comment**: Review authors did not specify which domains they considered key or critical to the overall study level assessment.	risk (plausible bias that raises some doubt about results). **For non-randomised controlled trials**: used ROBINS-I (7-domain tool) to assess RoB. An overall RoB assigned on basis of assessment of each domain as low, moderate, serious, or critical, with the minimum overall risk typically determined by the highest risk assigned in any individual domain. **RoB in included studies**: The most important reasons why studies were considered at high risk of bias was the lack of a washout period (or too short of a washout period) between diets in the crossover studies (n=13) or a high drop-out rate (n=8), or both and 1 study appeared to be quasi-randomised. **Overall study level assessment** RCTs: • High: 19 • Low: 0 • Unclear: 14 **Non-randomised controlled trials:** • Moderate: 1 • Serious: 2 **Comment**: Review authors did not specify which domains they considered key or critical

Systematic review (lead author, year)			
Huntriss et al (2018)	**Korsmo-Haugen et al (2018)**	**Sainsbury et al (2018)**	**van Zuuren et al (2018)**
	Authors reported: Because of the nature of the delivery of dietary interventions, blinding of participants and study personnel who provided dietary advice was not possible. Hence this item was not considered when assessing overall RoB.		to the overall study level assessment.

Table A13.2: Overall RoB in publications included in meta-analyses (36 publications)

Publication	**Systematic review** (lead author, year)		
	Korsmo-Haugen (2018)	**Sainsbury (2018)**	**van Zuuren (2018)**
Brehm (2009)	N/A	U	N/A
Brinkworth (2004)	U	N/A	N/A
Brunerova (2007)	N/A	H	N/A
Daly (2006)	H	L	N/A
Davis (2009)	U	U	U
de Bont (1981)	N/A	N/A	U
Elhayany (2010)	U	U	H
Esposito (2009)	N/A	N/A	N/A
Fabricatore (2011)	N/A	L	N/A
Facchini (2003)	H	N/A	N/A
Goday (2016)	N/A	N/A	U
Goldstein (2011)	U	N/A	N/A
Guldbrand (2012)	U	L	U
Hockaday (1978)	N/A	N/A	U
Jenkins (2014)	U	N/A	N/A
Jonasson (2014)	H	N/A	N/A
Krebs (2012)	L	L	N/A
Larsen (2011)	L	L	N/A
Luger (2013)	H	U	N/A
Mayer (2014)	N/A	N/A	N/A
McLaughlin (2007)	U	N/A	N/A
Nielsen (2005)	N/A	N/A	S
Parker (2002)	N/A	H	N/A
Pedersen (2014)	L	U	N/A
Samaha (2003)	H	L	H
Saslow (2014)	N/A	L	N/A
Shai (2008)	U	H	U
Stern (2004)	N/A	N/A	N/A
Tay (2014)	N/A	N/A	U
Tay (2015)	N/A	L	N/A
Tay (2018)	N/A	N/A	N/A*
Watson (2016)	N/A	U	N/A
Westman (2008)	H	H	N/A
Wolever (2008)	U	H	U
Wycherley (2010)	N/A	U	N/A
Yamada (2014)	N/A	U	U

H, high RoB; L, low RoB; U, unclear RoB; S, serious RoB (based on ROBINS-I); *N/A, not applicable.

Shaded cells indicate that the RoB assessment of a primary study differed between the SRs

Annex 14: Medication use

Table A14.1: Reported medication use in 36 publications (31 RCTs) included in MAs of prioritised SRs

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Brehm (2009) (n=124/95); 12 m	Inclusion criteria stipulated treatment by diet or oral agents only (no insulin).	Only modest changes with no systematic differences between groups.	Medication tracked in 32 out of 124 participants. Medication use discussed only in conclusions section as a limitation.	Descriptive
Brinkworth (2004) (n=64/38); 16 m (Note: same RCT as reported by Parker, 2002).	• Oral hypoglycaemic medications (n=17) • Insulin (n=3) • Anti-hypertensive medication (n=18) • Lipid-lowering drugs (n=16)	NR	Under 'Subjects and Methods,' medication usage listed for those who completed study (n=38).	NR
Brunerova (2007); (n=27); 3 m	Inclusion criteria stipulated treatment with diet or oral glucose-lowering drugs (no insulin).	NR		NR

Daly (2006) (n=102/79); 3 m	• Oral hypoglycaemic agents (40%)
	• Insulin (20%)
	• Combination of two (40%)
		Post-study analysis (75% of participants; self-reported)
		• Insulin
		  ○ reduced in 85% of insulin using participants in LC group and 22% in HC group
		  ○ increased in 5% of LC group and 16% in HC group
		• Oral hypoglycaemic agents: unchanged in both groups
			Post study analysis conducted because: 'key group workers reported an impression that medication requirements had reduced in low carbohydrate group.'	Descriptive

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**

Davis (2009) (n=105/91); 12 m	• Oral hypoglycaemic agents
	  ○ Metformin (LC, 78%; HC, 86%)
	  ○ Sulfonylurea (LC, 44%; HC, 52%)
	• Insulin (LC, 35%; HC, 24%)
	• Cholesterol-lowering medication (LC, 62%; HC, 56%)
		• Insulin: dose reduced by a mean (SD) of 10 (14) units in LC group and increased by 4 (19) units in HC group (p=0.12) at 12 m
		• Sulfonylureas: 26% reduction in sulfonylurea dose of 1.6 (3.6) mg in both arms at 12 m
			Pre-randomisation: diabetes medications adjusted to minimise side-effects that could affect findings, such as discontinuing thiazolidinediones (due to weight gain as side-effect) and changing short-acting insulin to insulin glargine to minimise risk of hypoglycaemia.
			At randomisation and during study: used predefined algorithm to adjust medications: reduced insulin by 50% and discontinued sulfonylurea in LC group and reduced insulin by 25% and decreased sulfonylurea dose by 50% in HC group.
			Subsequently algorithm for medication adjustment same in both groups.
			Metformin not adjusted.
				Statistical: between-group, no difference

de Bont (1981) (n=148/136); 6 m	• Oral hypoglycaemic drugs • Insulin	• Oral hypoglycaemic drugs: in LC group, n=10 received increased dosage • Insulin: in LC group, n=3 commenced		Descriptive

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Elhayany (2010) (n=259/179); 12 m	Inclusion criteria specified no change in diabetes medication for at least 3 m before entering study. Exclusion criteria specified current insulin treatment.	NR		NR
Esposito (2009) (n=215/195); 48 m	Only recruited newly diagnosed T2D individuals who had never been treated with anti-hyperglycaemic drugs. Exclusion criteria specified use of agents affecting glycaemic control. • Anti-hypertensive therapy: LC, 24%; HC, 23% • Lipid-lowering therapy: LC, 15%; HC, 16%	Significant difference between groups in need for anti-hyperglycaemic drug therapy • At 18 months: LC, 12% (95% CI 8, 16); HC 24% (95% CI, 18, 31) required treatment • At trial end: LC, -44% (95% CI, 34, 53); HC, 70% (95% CI, 62, 79) • Hazard ratio (HR)=0.63 (95% CI, 0.51, 0.86; p<0.001); HR adjusted for weight, 0.70 (95% CI, 0.59, 0.90; p<0.001)	Primary outcome measure was time to introduction of anti-hyperglycaemic drug therapy. Participants with HbA1c >7% given additional 3 m to reinforce dietary guidance and physical activity. If HbA1c remained >7%, a drug regimen was introduced.	Statistical: between-group, greater reduction in LC group
Fabricatore (2011) (n=79/50); 9 m	• Anti-diabetic medications (did not specify)	At 20 or 40 weeks: no difference between groups in % of participants who increased, decreased, did not change intensity of their diabetes medication regimen.	Medication use tracked throughout study and changes in anti-diabetic medications quantified: new medication or increased dosage from baseline (+1); no change in medications or dosages from baseline (0); or discontinued medication or decreased dosage from baseline (-1).	Descriptive

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Facchini (2003) (n=191/170); 3.9 y	• Insulin: LC, 49%; HC, 51% • Metformin: LC, 6%; HC, 5% • Sulfonylurea: LC, 23%; HC, 26% • Statins LC, 9%; HC, 8% Also listed aspirin, ASI, calcium antagonist, central adrenergic blocker, β-blocker, α-blocker, diuretics	• Insulin: LC, 47%; HC, 54% • Metformin: LC, 7%; HC, 8% • Sulphonylurea: LC, 19%; HC, 21% • Statins: LC, 10%; HC, 12%	All participants had various degrees of kidney failure.	Descriptive
Goday (2016) (n=89/76) 4 m	Exclusion criteria specified T2D participants receiving insulin Oral anti-diabetic drugs: LC group, 73%; HC group, 86%	• LC group: significant decrease in number of participants taking anti-diabetic drugs (73% to 50%; p=0.027 • HC group, not significant (86% to 83%; p=0.7)		Statistical: within-group, reduction in LC group, no change in HC group
Goldstein (2011) (n=52/30); 12 m	Inclusion criteria specified T2D participants not receiving insulin. • Anti-diabetic medication (did not specify).	Anti-diabetic medication not held constant during study and treatment changes differed modestly between groups.	In discussion, authors note 'Fear of hypoglycaemia necessitated the reduction of medication, limiting our ability to identify the effect of the diets on glucose values.'	Descriptive

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Guldbrand (2012) (n=61/54); 24 m (Note: same RCT as reported by Jonasson, 2014).	• Anti-diabetic medication (metformin, glibenclamide) • Insulin • Lipid-lowering (simvastatin, atorvastatin) At baseline, n=15 in LC group and n=13 in HC group on oral anti-diabetic medication only; 11 in HC group and 10 in LC were treated with insulin and oral medication.	• Anti-diabetic medication: no significant difference between groups • Insulin: no significant difference between groups in total dose. Reduction in insulin dose significant only in LC group at 6 months and between the 2 groups (p=0.046) • Lipid-lowering medications: no significant difference between groups	Reductions in oral anti-diabetic medication and insulin dose were made consecutively to avoid hypoglycaemia. Hypo-lipidaemic and anti-hypertensive medication adjusted to avoid CVD in study by physician for each patient at primary healthcare centre.	Statistical: within-group, no change in LC or HC group; between-groups, no difference
Hockaday (1978) (n=93/93); 12 m	Inclusion criteria specified newly diagnosed T2D adults who did not require either insulin or oral hypoglycaemic agents.	Not applicable	Not applicable	Not applicable
Jenkins (2014) (n=141/119); 3 m	• Anti-hyperglycaemic (all; 100%) • Includes metformin sulfonylurea, thiazolidinedione, injectable GLP-1 analogue • Cholesterol-lowering: LC group, 71%; HC group, 71% • BP lowering: LC group, 56%; HC group, 61%	• Oral anti-glycaemic medication: no significant difference between groups • Lipid-lowering medications: no significant difference between groups		Statistical: between-group, no difference

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Jonasson (2014) (n=61/61); 6 m (Note: same RCT as reported by Guldbrand, 2012).	• Oral glucose-lowering medications: 50% LC group; 42% HC group • Insulin: 10% LC group; 16% HC group • Oral glucose-lowering and insulin: 33% LC group; 35% HC group • Lipid-lowering: 73% LC group; 77% HC group	• Oral glucose-lowering medication: no change • Insulin: dose significantly reduced in LC group but not in HC group • Lipid-lowering: during study period, statin therapy initiated in 2 LC participants; hence n=24 in each group treated with statins at 6 m		Statistical: within-group, reduction in LC group, no change in HC group
Krebs (2012) (n=419/294); 24 m	• Diet only: LC, 19.3%; HC, 13.9%); all, 16.6% • Oral agents only: LC, 56%; HC, 57.4%; all, 56.7% • Insulin and oral agents: LC, 24.6%; HC, 28.7%; all, 26.7%	NR	For HbA1c and plasma glucose: differences over time estimated controlling for changes in glucose-lowering medication. For cholesterol, LDL, triacylglycerols, HDL: differences over time estimated controlling for changes in lipid-lowering medication.	NR
Larsen (2011) (n=108/99); 12 m	• None: LC, n=5 (9%); HC, n=5 (11%) • Insulin: LC, n=10 (19%); HC, n=7 (15%) • Oral anti-diabetic medication (did not specify): LC, n=38 (72%); HC, n=34 (74%)	Significantly greater reduction (p=0.05) in diabetes medication in LC group (mainly insulin and sulphonylurea).	Commonly cited reason for decreasing medication dosage was frequency of hypoglycaemic episodes. After adjusting for changes in medication, the between-group difference in HbA1c remained non-significant.	Statistical: between-group, greater reduction in LC group

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Luger (2013) (n=44/42); 3 m	• Insulin therapy: all • Additional oral anti-diabetic medication (n=31) • Lipid-lowering agents (n=26) • BP medication (n=40) • Anti-coagulants (n=19)	Insulin requirement significantly reduced in LC group (p=0.01) and slightly increased in HC group after 12 weeks and significantly different between groups (p=0.007). Combining study groups, weight loss over 12 weeks was associated with changes in insulin dose (p=0.000; r=0.6). No change in concomitant medications.		Statistical: within-group, reduction in LC group, no change in HC group; between-group, greater reduction in LC group
Mayer (2014) (n=46); 11 m	• Insulin +/- oral agents: LC group, n=7 (31.8%); HC group, n=8 (33.3%) • Oral agents only: LC group, n=12 (54.6%); HC group, n=14 (58.3%) • No agents: LC group, n=3 (13.6%); HC group, n=2 (8.3%)	Estimated medication effect score (MES). LC group led to greater reduction in anti-glycaemic medications. MES decreased by -1.24 (95% CI -1.80, -0.69) in LC group versus -0.82 (95% CI -1.33, -0.31) in HC+O group (p=0.27). Of the participants with complete medication data (LC, n=17; HC+O, n=23) 70.6% of LC versus 30.4% of HC+O had decreases in MES ≥50% (p=0.01).	In both arms anti-glycaemic medications were individually adjusted following an algorithm to prevent hypoglycaemia. A MES assessed overall utilisation of anti-glycaemic agents (based on medication potency and total daily dose). MES was a primary outcome of study.	Statistical: within-group, reduction in LC group and in HC group; between-group, no difference
McLaughlin (2007) (n=29/29); 3m	Inclusion criteria specified 'no use of anti-hyperglycaemic medications'.	Not applicable		NR

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**

Nielsen (2005) (n=31/31); 6 m	• Insulin: LC, n=11; HC, n=6
	• Metformin LC, n=11; HC, n=10
	• Sulfonylurea: LC, n=5; HC, n=5
		• Insulin requirement
		  ○ LC: mean requirement decreased from 60 ± 33 to 39 ± 21 IU/d in 1st week and n=2 able to discontinue insulin within 24 weeks. Average requirement after 24 weeks was 18 ± 11 IU/d
		  ○ HC group: slight increase in mean insulin requirement during the 24 weeks
		• Sulphonylurea
		  ○ LC: n=2 discontinued, other 3 reduced doses because of episodes of hypoglycaemia
		  ○ HC group: n=1 discontinued
		• Metformin: NR
				Descriptive

Parker (2002) (n=64/54); 3 m (Note: same RCT as reported by Brinkworth, 2004).	• Oral hypoglycaemic agents (metformin, sulfonylureas or combination of both): 48% • Insulin: 7% • Anti-hypertensive or lipid-lowering medications (% NR)	Hypoglycaemic medications: decreases in dosage occurred in 8 participants at weeks 4 and 8 (LC, n=5; HC, n=3).	Participants on anti-hypertensive or lipid-lowering medication asked to maintain the same dose throughout the study.	Descriptive

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Pedersen (2014) (n=76/45); 12 m	• Oral blood glucose lowering medicine and/or insulin: metformin (n=17), metformin + sulfonylurea (n=10), metformin + glitazones (n=2), metformin + sulfonylurea + glitazones (n=3), metformin + insulin glargine (n=6), metformin+sulfonylurea + insulin Novomix + mixtard (n=3) • Statins: monotherapy (n=38), both statin and ezetimibe (n=5), ezetimibe monotherapy (n=1)	• Oral blood glucose lowering medications o LC: 3 stopped, 3 decreased dose, 4 increased dose; 4 changed to other medication o HC: 4 decreased, 4 increased; 2 changed to other medication • Statins: dose decreased n=1 (LC), increased n=4 (1 LC and 3 HC), stopped n=5 (3 LC and 2 HC); changed to other medication n=3 (2 LC; 1 HC	When data for LDL cholesterol analysis confined to those who did not change medication, no effect of diet seen on LDL cholesterol.	Descriptive
Samaha (2003) (n=52/29); 6 m (Note: same RCT as reported by Stern, 2004).	• Hypoglycaemic agents: sulfonylurea (LC, 11%; HC, 16%), metformin (LC, 17%; HC, 13%) • Insulin (LC, 9%; HC, 4%) • Anti-hypertensive medications (LC, 64%; HC, 57%) • Peroxisome proliferator–activated receptor gamma agonist (LC, 2%; HC, 2%) • Lipid-lowering medication: statins (LC, 42%; HC, 37%), gemfibrozil (LC, 3%; HC, 0%)	• Hypoglycaemic agents or insulin: at 6 m, n=7 in LC group had dose reductions in oral hypoglycaemic agents or insulin; in comparison 1 participant in HC group had a dose reduction in insulin and 1 began oral therapy • Lipid-lowering medications: no changes in HC group, n=2 in LC started taking a statin and 1 stopped • Anti-hypertensive medications: no change		Descriptive

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Saslow (2014) (n=34/32); 3 m	Excluded individuals using insulin or more than 3 hypoglycaemic medications. • Metformin only (LC, 31%; MC, 44%) • Metformin and another oral diabetes agent (sulfonylurea, thiazolidinediones) (LC, 44%; HC, 28%)	Discontinued 1 or more oral diabetes medications: LC (44%; n=7) versus HC (11%; n=2) (p=0.03).		Statistical: between-group, more discontinued in LC group
Shai (2008) (n=46/36); 24 m	• Insulin (1%) • Oral glycaemic control medications (8%) • Lipid-lowering (26%) • Anti-hypertensive (30%)	Little change in medication use. No significant differences among groups in amount of change. • Glycaemic control: n=5 initiated medications for glycaemic control and n=1 reduced dosage • Lipid-lowering: n=4 initiated and n=3 stopped • Anti-hypertensive: n=20 initiated treatment		Statistical: between-group, no difference

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Stern (2004) (n=54/34); 12 m (Note: same RCT as reported by Samaha, 2003).	• Diabetes medications: sulfonylureas (LC, 11%; HC, 16%), metformin (LC, 17%, HC, 13%), insulin (LC, 9%, HC, 6%), peroxisome proliferator-activated receptor-γ agonist (LC, 2%; HC, 2% • Anti-hypertensive drugs: LC, 64%; HC, 57% • Hyperlipidaemia medications: statins (LC, 42%, HC, 37%), gemfibrozil (LC, 3%, HC, 2%)	NR		NR
Tay (2014) (n=115/93); 6 m	• Insulin • Oral anti-diabetic medication: metformin, sulfonylureas, thiazolidinediones, GLP-1 agonists, DPP-4 inhibitors • Lipid-lowering medication • Anti-hypertensive medication	• Anti-glycaemic MES o 2-fold greater reduction in LC versus HC group; more participants in LC group experienced reduction >20% compared with HC group ($p<0.005$) • Lipid-lowering medication: o LC, n=4 decreased, n=3 increased o HC, n=2 increased, n=2 increased • Anti-hypertensive medication: o LC, n=10 decreased, n=3 increased o HC, n=1 decrease, n=3 increased	Changes in diabetes medication requirements quantified by anti-glycaemic MES, which was computed on basis of potency and dosage of diabetes medications. At baseline, medication use and anti-glycaemic MES were similar in both groups.	Statistical: between-group, greater reduction in LC group

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**

Tay (2015) (n=115/78); 12 m
(Note: same RCT as reported by Tay, 2014).
	As above	• Anti-glycaemic MES:
		  ○ Greater reduction in LC versus HC group (p=0.02); LC, 52% and HC, 21% experienced ≥20% in anti-glycaemic MES (p<0.01)
		• Lipid-lowering medication:
		  ○ LC, n=4 decreased, n=3 increased
		  ○ HC, n=6 increased, n=1 increased
		• Anti-hypertensive medication:
		  ○ LC, n=13 decreased, n=2 increased
		  ○ HC, n=8 decrease, n=1 increased
			As above	Statistical: between-group, greater reduction in LC group

Tay (2018) (n=115/61); 24 m
(Note: same RCT as reported by Tay, 2014).
	As above	• Anti-glycaemic MES:
		  ○ Greater reduction in LC group, -0.5 (95% CI -0.6, -0.3) versus HC group -0.2 (95% CI -0.4, -0.02) (p=0.03)
		  ○ Over twice the number of LC participants (n=22) had a 20% reduction in MES compared to HC participants (n=9)
			As above	Statistical: between-group, greater reduction in LC group

Watson (2016) (n=61/44); 6 m	• Oral anti-diabetic medications: metformin (LC, 58%; HC, 64%), sulfonylureas (LC, 16%; HC, 18%), GLP-1 agonists (LC, 7%; HC, 7%), DPP-4 inhibitors (LC, 7%; HC, 11%) • Insulin (LC, 19%; HC, 21%) • Lipid-lowering (LC, 52%; HC, 64%) • Anti-hypertensive (LC, 61%; HC, 43%)	• Diabetes medication: MES decreased over time (p=0.02), with no significant difference between the groups (p=0.43) • Lipid-lowering medication: LC, n=1 decreased, n=1 increased; HC, n=3 decreased • Anti-hypertensive medication: dosage reduced (LC, n=5; HC, n=2) and increased for n=1 in HC group	Changes in medication use quantified by MES (basis for this not given).	Statistical: within-group, reduction in LC and in HC groups; between-group, no difference

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Westman (2008) (n=84/50); 6 m	• Hypoglycaemic medications: ○ LC (n=20; 95.2%) (insulin only, n=4, oral agents only, n=12; insulin and oral agents n=4) ○ HC (n=22; 75.9%) (insulin only, n=3, oral agents only, n=19)	20/21 (95%) participants in LC group eliminated or reduced medication compared with 18/29 (62%) in HC group ($p<0.01$). 5 individuals (LC, n=4; HC, n=1) who were taking >20 units of insulin at baseline were no longer taking insulin at end of study.		Statistical: between-group, more eliminated/reduced in LC group
Wolever (2008) (n=162/130); 12 m	Exclusion criteria specified insulin or hypoglycaemic / anti-hyperglycaemic medication use. • Anti-hypertensive: ACE inhibitor (48%); diuretic (16%); calcium channel blocker (12%); angiotensin-receptor blocker (11%); β-blocker (9%); α-blocker (3%) • Lipid-lowering medication (43%)	Doses of lipid-lowering drugs were adjusted.	Doses of lipid-lowering drugs adjusted during run-in for optimal control, then kept constant unless changes required for clinical reasons. Participants whose dose of statin changed during study (n=15) were excluded from analysis of blood lipids and lipoproteins.	Descriptive
Wycherley (2010) (n=40/28); 4 m	• Hypoglycaemic (LC, n=7; HC, n=11) • Lipid-lowering (LC, n=5; HC, n=9) • Anti-hypertensive (LC, n=4; HC, n=9)	• Hypoglycaemic medication: difference between groups not significant • Lipid-lowering medication: no change • Anti-hypertensive medication: no change	Lipid-lowering and anti-hypertensive medications encouraged to remain constant throughout the intervention.	Statistical: between-group, no difference

Study (year) (participant no. at baseline/completers); duration	**Medication type at baseline**	**Changes**	**Comments**	**Summary**
Yamada (2014) (n=24/24); 6 m	• Glucose-lowering drugs (LC/HC): o Insulin (25/33%) o Oral agents: metformin (42/8%); sulfonylurea (42/67%), glinide (8/0%), thiazolidinedione (33/50%), α-glucosidase inhibitor (17/0%), DPP-4 inhibitor (17/25%).	In LCD group, n=3 treated with a sulfonylurea or insulin, experienced symptomatic hypoglycaemia; the events did not recur after adjusting the medications.	Did not change medications unless hypoglycaemia occurred.	Descriptive

Table A14.2 Observations from 3 prioritised SRs with MAs* on medication change

Systematic review	Narrative summary of medication changes
Sainsbury et al (2018)	Reported that carbohydrate restriction either reduced the dosage of oral medications and/or insulin or eliminated medication for participants across all studies that reported on medication outcomes. They noted that many studies allowed medication changes throughout the intervention due to potential for hypoglycaemic episodes on carbohydrate-restricted diets. While some studies recognised the potential confounding effect of medication change and corrected for this in analysis, the majority either did not specify or stated they did not make adjustments for medication change. This may have attenuated the positive effect of carbohydrate restriction on glycaemic control. They concluded that although there were inconsistencies in the measurement and reporting of diabetes medications across studies, the results suggested that carbohydrate-restricted diets are associated with a reduction in medication dosage.
Korsmo-Haugen et al (2018)	Reported that the limited information from the included studies suggested a greater reduction in use of diabetes medication (mainly insulin) that may have masked a more positive impact on glycaemic control than shown in their MA. Some studies repeated their analyses adjusting for difference in medication and found it did not alter the conclusions.
van Zuuren et al (2018)	Reported that medication regimes (glucose-, BP and lipid-lowering) were modified in some studies but remained unchanged in others. Some studies included medication naïve patients while others did not document medication details adequately. Out of 5 studies that included patients taking medication and that adequately reported changes,4 reported that glucose-lowering drug doses were reduced in participants on LCDs but not in those on HCDs. Inconsistent methods of quantification and reporting precluded reliable statistical analysis of changes in drug doses.

*Huntriss et al (2018) not included here because medication change was assessed as an outcome (see chapter 5 in report).

Annex 15: Results of meta-analyses in prioritised systematic reviews

Table A15.1A: Body weight (≥3 to 6 m)

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Sainsbury et al (2018)				
3 m Main analysis	-1.08 (-1.93, -0.23), p=0.01; I^2=69% 12 RCTs (n=791)	Yes	high (4); low (3); unclear (5)	
Subgroup analysis (by CHO quantity)	low vs high CHO (32.5% weight) -2.47 (-3.33, -1.60), p<0.00001; I^2=0% 4 RCTs (n=268)	Yes	high (1); low (2); unclear (1)	Out of 4 RCTs in low CHO subgroup, reported CHO intakes were moderate in 2 RCTs.
	Moderate vs high CHO (67.5% weight) 0.14 (-0.30, 0.59), p=0.53; I^2=0% 8 RCTs (n=523)	No	high (3); low (1); unclear (4)	Out of 8 RCTs in moderate CHO subgroup, reported CHO intakes were high in 2 RCTs (1 did not report intakes).
6 m Main analysis	-0.14 (-0.94, 0.65), p=0.72; I^2=48% 9 RCTs (n=953)	No	high (3); low (2); unclear (4)	Included 1 RCT (Strychar, 2009) with T1D participants (n=30, 11.7% weight in MA)
Subgroup analysis (by CHO quantity)	low vs high CHO (32.5% weight) -1.07 (-2.52, 0.37), p=0.14; I^2=33% 4 RCTs (n=240)	No	high (1), low (1), unclear (2)	Out of 4 RCTS in the low CHO subgroup, reported CHO intakes were moderate in 3 RCTs.
	Mod vs high CHO (67.5% weight) 0.29 (-0.60, 1.17), p=0.52; I^2=48% 5 RCTs (n=713)	No	high (2), low (1), unclear (2)	Included 1 RCT (Strychar, 2009) of adults with T1D (see above)

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
van Zuuren et al (2018)				
4 to 6 m Main analysis	-2.51 (-5.42, 0.40), p=0.09; I^2=88% 7 RCTs (n=537)	No	unclear (6), high (1)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	0.52 (-0.28, 1.33), p=0.2, I^2=0% 5 RCTs (n=417)	No	unclear (5)	
Sensitivity analysis (excluding studies at high RoB)	-1.69 (-4.57, 1.18), p=0.25; I^2= 88% 6 RCTs (n=506)	No	unclear (6)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (43.8% weight)	-0.87 (-1.88, 0.15), p-value NR; I^2=33% 7 RCTs (n=424)	No	high (5), unclear (2)	
Huntriss et al (2018)	Did not perform MA at 3 and 6 m			
3 m Main analysis	3 out of 5 RCTs reported significant difference in weight change in favour of LCD; 2 reported no difference between groups.	N/A	high in 15 of 18 studies in ≥1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies	
6 m Main analysis	4 out of 8 RCTs reported significant difference in weight change in favour of LCD; 4 reported no difference between groups.	N/A	as above	

Table A15.1B: Body weight (≥12 m)

Author (year)/analysis	Results mean difference (MD) change (kg) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Sainsbury et al (2018)				
Main analysis	-0.43 (-0.93, 0.07), p=0.09; I^2=0% 10 RCTs (n=1267)	No	high (1), low (4), unclear (4), missing (1)	
Subgroup analysis (by CHO quantity)	low vs high CHO (13% weight) 0.58 (-0.83, 1.99), p=0.42; I^2=0% 3 RCTs (n=244)	No	unclear (1), low (2)	In low vs high CHO subgroup analysis (3 RCTs), reported CHO intakes were moderate vs high in 2RCTs and low vs high in 1 RCT.
	Moderate vs high CHO (87% weight) -0.58 (-1.11, -0.04), p=0.04; I^2=0%, 7 RCTs (n=1023)	Yes	high (1), unclear (3), low (2), missing (1)	In the moderate vs high CHO subgroup analysis (7 RCTs), reported CHO intakes were high vs high in 2 RCTs; moderate vs high in 3 RCTs and moderate vs moderate in 1 RCT; (1 NR).
Korsmo-Haugen et al (2018)				
Subgroup analysis (by study duration; 56% weight)	0.14 (-0.29, 0.57), p-value NR; I^2=0% 10 RCTs (n=1163)	No	high (1), low (3), unclear (6)	
Huntriss et al (2018)				
Main analysis	0.28 (-1.37, 1.92), p=0.74; I^2=75% 6 RCTs (n=567)	No	high in 15 of 18 studies in ≥1 of 6 criteria. High risk of performance bias in 15/18 (83%) studies.	
Van Zuuren et al (2018)				
Main analysis	-0.19 (-1.65, 1.27), p=0.80; I^2=0% 5 RCTs (n=483)	No	unclear (4), high (1)	
Sensitivity analysis (excluding studies at high R0B)	0.12 (-1.53, 1.76), p=0.69; I^2= 0% 4 RCTs (n=367)	No	unclear (4)	

Table A15.2A: HbA1c (≥3 to 6m)

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Sainsbury et al (2018)				
3 m Main analysis	-0.19 (-0.33, -0.05), p=0.008; I^2=28% 12 RCTs (n=791)	Yes	high (4); low (3); unclear (5)	
Subgroup analysis (by CHO quantity)	low vs high CHO (26% weight) -0.47 (-0.71, -0.23), p=0.0001; I^2=0% 4 RCTs (n=268)	Yes	high (1); low (2); unclear (1)	Out of 4 RCTs in low CHO subgroup, reported CHO intakes were moderate in 2 RCTs.
	Moderate vs high CHO (74% weight) -0.06 (-0.17, 0.06), p=0.33; I^2=0% 8 RCTs (n=523)	No	high (3); low (1); unclear (4)	Out of 8 RCTs in moderate CHO subgroup, reported CHO intakes were high in 2 RCTs (1 NR).
Sensitivity analysis (excluding studies with significantly greater weight loss on LCD)	-0.05 (-0.17, 0.06), p =0.35; I^2=0% 7 RCTs (n=481)	No	high (3); low (1); unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	-0.25 (-0.42, -0.07), p-value NR; I^2=NR 8 RCTs (n=552)	Yes	low (3); unclear (5)	

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Sainsbury et al (2018)				
6 m Sensitivity analysis (excluding 1 RCT of adults with T1D)	-0.19 (-0.35, -0.02), p-value NR; I^2=44% 10 RCTs (n=1054)	Yes	high (2); low (4); unclear (4)	Results of main analysis not reported here because included 1 RCT of adults with T1D (Strychar, 2009).
Subgroup analysis (by CHO quantity)	<u>low vs high CHO</u> (26% weight) -0.36 (-0.62, -0.09), p=0.008; I^2=0% 5 RCTs (n=295)	Yes		In low vs high subgroup analysis, reported CHO intakes were moderate in 3 out of the 5 RCTs. Results of subgroup analysis for moderate vs high CHO not reported here because included 1 RCT of adults with T1D (Strychar, 2009).
6 m Sensitivity analysis (excluding studies at high RoB)	-0.21(-0.38, -0.05), p-value NR; I^2=NR 8 RCTs (n=896)	Yes	low (4); unclear (4)	Results of 6 m sensitivity analysis omitting studies with significantly greater weight loss on low CHO diets not included here because included Strychar (2009) (see above).

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Van Zuuren et al (2018)				
4 to 6 m Main analysis	-0.26% (-0.50, -0.02), p=0.04; I^2 =59% 7 RCTs (n=539)	Yes	serious (1); unclear (6)	
Sensitivity analysis (fixed-effects model)	-0.23% (-0.38, -0.09), p=0.001; I^2 =59% 7 RCTs (n=539)	Yes	serious (1); unclear (6)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	-0.42% (-0.61, -0.24), p<0.00001; I^2 =0% 5 RCTs (n=310)	Yes	serious (1); unclear (4)	
Sensitivity analysis (excluding studies at high RoB)	-0.20% (-0.44, 0.04), p=0.1; I^2 =55% 6 RCTs (n=508)	No	unclear (6)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (46.8% weight)	-0.17% (-0.27, -0.08), p-value: NR; I^2= 0% 6 RCTs (n=395)	Yes	high (5), unclear (1)	Also performed subgroup analysis of low and moderate CHO studies but did not separate shorter and longer-term studies.

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Huntriss et al (2018)	Did not perform MA at 3 and 6 m			
3 m Main analysis	5 out of 7 RCTs reported average difference of ≥0.2% favouring LCD with 3 of these reporting a difference of ≥0.5%. Remaining 2 studies reported no difference between groups. 2 studies reported a statistically significant difference in favour of the low CHO group ($p<0.05$); however, when 1 of these studies adjusted results for differences in baseline HbA1c, statistical significance was lost ($p=0.06$).	N/A	high in 15 of 18 studies in ≥1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies	
6 m Main analysis	7 out of 8 RCTs reported improvement of ≥0.2% in favour of LCD with 3 reporting improvements ≥0.5%. The remaining study reported no difference between groups. 4 studies reported a statistically significant difference between groups in favour of the LCD; 1 study reported that statistical significance lost after taking account of differences in baseline HbA1c.	N/A	as above	

Table A15.2B: HbA1c (≥12 months)

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Sainsbury et al (2018)				
12 m Main analysis	-0.09 (-0.21, 0.03), p=0.12; I^2=16% 12 RCTs (n=1403)	No	high (1), low (5), unclear (4); missing (2)	
Subgroup analysis (by CHO quantity)	low vs high CHO (18% weight) -0.17 (-0.44, 0.09), p=0.19; I^2=0% 4 RCTs (n=301)	No	low (2), unclear (1), missing (1)	In low vs high subgroup analysis, reported intake was moderate in 3 out of 4 RCTs.
	Moderate vs high CHO (82% weight) -0.08 (-0.23, 0.06), p=0.25; I^2=30% 8 RCTs (n=1102)	No	high (1), low (3), unclear (3), missing (1)	In moderate vs high subgroup analysis, actual intake was high in 2 out of the 8 RCTs.
Sensitivity analysis (excluding studies at high RoB)	-0.13 (-0.26, -0.01), p-value NR; I^2=NR 11 RCTs (n=1438)	Yes	how (5), unclear (4); missing (2)	
	low vs high CHO (% weight NR) -0.17 (-0.44, 0.09), p-value NR; I^2=NR 4 RCTs (n= 297)	No	low (2), unclear (1); missing (1)	Details of the studies included in this analysis not provided so unable to check reported CHO intakes in the low and moderate categories.
	Moderate vs high CHO (% weight NR) -0.13 (-0.30, 0.03), p-value NR; I^2=NR 7 RCTs (n=682)	No	low (3), unclear (3), missing (1)	High risk of bias study (Wolever, 2008) is deleted for this sensitivity analysis.
24 m Main analysis	-0.11 (-0.38, 0.15), p=NR; I^2=NR 3 RCTs (n=526)	No	NR	Results reported in narrative; details not provided.
Korsmo-Haugen et al (2018)				
≥12 m Subgroup analysis by duration (53% weight)	4.05 (-0.10, 0.09), p-value: NR; I^2=0% 10 RCTs (n=1030)	No	low (3), unclear (7)	
Huntriss et al (2018)				
12 m Main analysis	-0.28 (-0.53, -0.02), p=0.03; I^2=54% 7 RCTs (n= 645)	Yes	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Author (year)/analysis	Results mean difference (MD) change (%) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Van Zuuren et al (2018)				
≥12 m Main analysis	-0.36 (-0.58, -0.14), p=0.001; I^2=0% 4 RCTs (n=390)	Yes	high (1), unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	-0.25 (-0.66, 0.15), p=0.22; I^2=0% 3 RCTs (n=274)	No	unclear (3)	
24 m Main analysis	0.02 (-0.37, 0.41), p=0.93; I^2=13% 3 RCTs (n=199)	No	unclear (3)	
Sensitivity analysis (fixed-effects model)	0.06 (-0.27, 0.39), p=0.74; I^2=13% 3 RCTs (n=199)	No	unclear (3)	

Table A15.3: Fasting plasma glucose (≥3 to 6 months and ≥12 months)

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Shorter-term (≥3 to 6 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	-0.51 (-0.91, -0.12), p=0.01; I^2 =71%, 6 RCTs (n=396)	Yes	serious (1), unclear (5)	
Sensitivity analysis (fixed-effects model)	-0.27 (-0.38, -0.16), p<0.00001; I^2 =71% 6 RCTs (n=396)	Yes	serious (1), unclear (5)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	-0.76 (-1.05, -0.47), p<0.00001; I^2 =0% 4 RCTs (n=167)	Yes	serious (1), unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	-0.41 (-0.78, -0.03), p=0.03; I^2 =67% 5 RCTs (n=365)	Yes	unclear (5)	
Longer-term (≥12 m)				
van Zuuren et al (2018)				
≥12 m Main analysis	-0.37 (-1.22, 0.48), p=0.39; I^2= 92% 4 RCTs (n=340)	No	high (1), unclear (3)	
Sensitivity analysis (fixed-effects model)	-0.51 (-0.72, -0.30), p<0.00001; I^2= 92% 4 RCTs (n=340)	Yes	high (1), unclear (3)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	Results not considered (only 2 primary studies in MA)	N/A	N/A	
Sensitivity analysis (excluding studies at high RoB)	-0.05 (-1.11, 1.02), p=0.93; I^2= 92% 3 RCTs (n=224)	No	unclear (3)	
24 m Main analysis	Results not considered (only 2 primary studies in MA)	N/A	N/A	

Table A15.4: Serum total cholesterol (≥3 to 6 months and ≥12 months)

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Shorter-term (≥3 to 6 m)				
Korsmo-Haugen et al (2018) **3 to 6 m** Subgroup analysis by duration (24% weight)	-0.06 (-0.41, 0.30), p-value: NR; I^2= 57% 4 RCTs (n=279)	No	high (2), unclear (2)	
Longer-term (≥12 m)				
Korsmo-Haugen et al (2018) **>12 m** Subgroup analysis by duration (76% weight)	0.07 (-0.04, 0.19), p-value: NR; I^2= 23% 10 RCTs (n=1094)	No	high (1), low (3), unclear (6)	
Huntriss et al (2018) **12 m** Main analysis	-0.08 (-0.23, 0.08), p=0.35; I^2=60% 7 RCTs (n=645)	No	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Table A15.5: Serum triacylglycerol (≥3 to 6 months and ≥12 months)

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Shorter-term (≥3 to 6 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	-0.22 (-0.37, -0.08), p=0.002; I^2=41% 6 RCTs (n=508)	Yes	unclear (6)	
Sensitivity analysis (fixed-effects model)	-0.22 (-0.32, -0.11), p<0.0001; I^2=41% 6 RCTs (n=508)	Yes	unclear (6)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (31% weight)	-0.18 (-0.36, 0.00), p-value: NR; I^2=20% 7 RCTs (n=424)	-	high (5), unclear (2)	Significance not reported. To note: upper CI=0.
Longer-term (≥12 m)				
Korsmo-Haugen et al (2018)				
>12 m Subgroup analysis by duration (69% weight)	-0.10 (-0.23, 0.03), p-value: NR; I^2=61% 9 RCTs (n=967)	No	low (3), unclear (6)	
Huntriss et al (2018)				
12 m Main analysis	-0.24 (-0.35, -0.13), p<0.0001; I^2=0% 7 RCTs (n=645)	Yes	high in 15 of 18 studies in ≥1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Van Zuuren et al (2018)				
≥12 m Main analysis	-0.25 (-0.47, -0.04), p=0.02; I^2= 73% 5 RCTs (n=468)	Yes	high (1), unclear (4)	
Sensitivity analysis (fixed-effects model)	-0.25 (-0.36, -0.15), p<0.00001; I^2= 73% 5 RCTs (n=468)	Yes	high (1), unclear (4)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	-0.14 (-0.26, -0.02), p=0.02; I^2= 0% 4 RCTs (n=352)	Yes	unclear (4)	
Sensitivity analysis (excluding studies at high RoB)	As above	Yes	unclear (4)	
24 m Main analysis	Results not considered (only 2 RCTs in MA)	N/A	N/A	

Table A15.6: Serum LDL cholesterol (≥3 to 6 months and ≥12 months)

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Shorter-term (≥3 to 6 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	0.02 (-0.09, 0.13), p=0.75; I^2= 0% 5 RCTs (n=372)	No	unclear (5)	
Sensitivity analysis (fixed-effects model)	As above	No	unclear (5)	
Korsmo-Haugen et al (2018)				
3 to 6 m Subgroup analysis by duration (34% weight)	-0.08 (-0.29, 0.14), p-value: NR; I^2= 50% 6 RCTs (n=345)	No	high (4), unclear (2)	
Longer-term (≥12 m)				
Korsmo-Haugen et al (2018)				
>12 m Subgroup analysis by duration (66% weight)	0.03 (-0.10, 0.16), p-value: NR; I^2= 51% 9 RCTs (n=1064)	No	high (1), low (3), unclear (5)	
Huntriss et al (2018)				
12 m Main analysis	0.05 (-0.10, 0.19), p=0.54; I^2=0% 5 RCTs (n=389)	No	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Van Zuuren et al (2018)				
≥12 m Main analysis	-0.07 (-0.23, 0.09), p=0.41; I^2= 50% 4 RCTs (n=375)	No	high (1), unclear (3)	
Sensitivity analysis (fixed-effects model)	-0.08 (-0.20, 0.03), p=0.15; I^2= 50% 4 RCTs (n=375)	No	high (1), unclear (3)	
Sensitivity analysis (excluding studies causing substantial heterogeneity/high RoB)	4.05 (-0.14, 0.15), p=0.95; I^2= 0% 3 RCTs (n=259)	No	unclear (3)	

Table A15.7: Serum HDL cholesterol (≥3 to 6 months and ≥12 months)

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Shorter-term (≥3 to 6 m)				
van Zuuren et al (2018)				
4 to 6 m Main analysis	0.09 (-0.03, 0.22), p=0.13; I^2=91% 6 RCTs (n=508)	No	unclear (6)	
Sensitivity analyses (fixed-effects model)	-0.01 (-0.04, 0.02), p=0.43; I^2=91% 6 RCTs (n=508)	No	unclear (6)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	0.17 (0.11, 0.23), p<0.00001; I^2=0% 4 RCTs (n=283)	Yes	unclear (4)	
Sensitivity analysis (excluding studies at high RoB)	0.09 (-0.03, 0.22), p=0.13; I^2=91% 6 RCTs (n=508)	No	unclear (6)	

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Korsmo-Haugen et al (2018) **3 to 6 m** Subgroup analysis by duration (34% weight)	-0.01 (-0.07, 0.04), p-value: NR; I^2=15% 6 RCTs (n=345)	No	high (4), unclear (2)	

Author (year)/analysis	Results mean difference (MD) change (mmol/L) (95% CI), p-value; I^2 number of studies (participants)	Significant	Risk of bias (RoB) (author assessment)	Comments
Longer-term (≥12 m)				
Korsmo-Haugen et al (2018)				
>12 m Subgroup analysis by duration (68% weight)	0.06 (-0.01, 0.13), p-value: NR; I^2=71% 10 RCTs (n=1093)	No	high (1), low (3), unclear (6)	
Huntriss et al (2018)				
12 m Main analysis	0.06 (0.04, 0.09), p<0.00001; I^2=1% 7 RCTs (n=645)	Yes	high in 15 of 18 studies in ≥ 1 of the 6 criteria. High risk of performance bias in 15/18 (83%) studies.	
Van Zuuren et al (2018)				
≥12 m Main analysis	0.11 (0.05, 0.18), p<0.0007; I^2= 66% 4 RCTs (n=375)	Yes	high (1), unclear (3)	
Sensitivity analysis (fixed-effects model)	0.13 (0.10, 0.17), p<0.00001; I^2=66% 4 RCTs (n= 375)	Yes	high (1), unclear (3)	
Sensitivity analysis (excluding studies causing substantial heterogeneity)	0.08 (0.03, 0.13), p=0.001; I^2=0% 3 RCTs (n=259)	Yes	unclear (3)	
Sensitivity analysis (excluding studies at high RoB)	As above	Yes	unclear (3)	
24 m Main analysis	Results not considered (only 2 RCTs in MA)	N/A	N/A	

Annex 16: Evidence grading

Table A16.1A: Body weight, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	3m: Sainsbury (12 RCTs, n=791) 6m: Sainsbury (9 RCTs, n=953).
Results of MA (mean difference in change, %)	Significantly greater reduction in body weight in the lower CHO group at 3m but not at 6m At 3m: -1.08 (-1.93, -0.23), p=0.01 At 6m: -0.14 (-0.94, 0.65), p=0.72 (includes 1 RCT with T1D participants)
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> At 3m: • agreed with results of subgroup analysis (by CHO quantity) for low vs high CHO diet: -2.47 (-3.33, -1.60), p<0.00001; I^2=0%; but disagreed with subgroup analysis of moderate vs high CHO diet: 0.14 (-0.30, 0.59), p=0.53; I^2=0% • disagreed with results of Sainsbury at 6m and with results from van Zuuren (7 RCTs, n=537) and Korsmo-Haugen (7 RCTs, n=424) which all reported no difference in effect at 3 to 6m. At 6m: • agreed with results from van Zuuren (7 RCTs, n=537) and Korsmo-Haugen (7 RCTs, n=424) which both showed no difference in effect at 3 to 6m. <u>Heterogeneity</u> • Sainsbury: 3m, I^2=69%; Sainsbury: 6m, I^2=48%; van Zuuren: I^2=88%; Korsmo-Haugen: I^2=33% <u>Overlap</u> 1 RCT in all 3 MAs; Korsmo-Haugen: 3/7 RCTs in Sainsbury, 1/7 in van Zuuren; van Zuuren: 3/7 RCTs in Sainsbury, 1/7 RCTs in Korsmo-Haugen.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> 9/12 RCTs in Sainsbury at 3m were either at unclear or high risk of bias. 7/9 RCTs in Sainsbury at 6m were either at unclear or high risk of bias. Sainsbury at 3 m, ITT in 33% of RCTs (including 2 RCT that did not report type of analysis); at 6 m, ITT in 56% of RCTs.
Comments	
Difference in effect/Overall grade	**Inconsistent**

Table A16.1B: Body weight, longer term (≥ 12 m)

MA with largest number of RCTs/sample size	Korsmo-Haugen (10 RCTs, n=1163) Sainsbury (10 RCTs, n=1267)
Results of MA (mean difference in change, kg)	No difference in effect between lower and higher CHO groups. Korsmo-Haugen: 0.14 (-0.29, 0.57); p=NR Sainsbury: -0.43 (-0.93, 0.07); p=0.09
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from the 2 other MAs (Huntriss and van Zuuren) in agreement (no difference in effect). • Results from 1 subgroup analysis by Sainsbury moderate vs higher CHO group, not in agreement: significantly greater reduction in weight in the moderate compared to higher CHO group: -0.58 (-1.11, -0.04), p=0.04, I^2=0% Heterogeneity • I^2=0% in both Korsmo-Haugen and Sainsbury Overlap 8/10 RCTs in both Korsmo-Haugen and Sainsbury; 4/6 RCTs in van Zuuren, in Korsmo-Haugen and Sainsbury (same RCTs for both); 3/6 RCTs in Huntriss, in Korsmo-Haugen and Sainsbury.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA (higher vs poorer quality RCTs) • risk of bias (assessed by publication author)	Risk of bias • Korsmo-Haugen, unclear or high in 7 RCTs • Sainsbury, unclear or high in 5 RCTs (missing for 1 RCT) Analysis Korsmo-Haugen, ITT in 60% of RCTs (including 1 RCT that did not report type of analysis); Sainsbury, ITT in 50% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A16.2A: HbA1c, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	3m: Sainsbury (12 RCTs, n=791) 6m: Sainsbury (10 RCTs, n=1054)
Results of MA (mean difference in change, %)	Significantly greater reduction in HbA1c in the lower CHO group. At 3m: -0.19 (-0.33, -0.05), p=0.008 At 6m: -0.19 (-0.35, -0.02), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from Korsmo-Haugen (6 RCTs, n=395) and van Zuuren (7 RCTs, n=539) in agreement (significantly greater reduction). • Results from subgroup analyses by Sainsbury (3 and 6m) lower vs higher CHO diet in agreement with main analysis (significantly greater reduction) moderate vs higher CHO diet (3m) disagreed: -0.06 (-0.17, 0.06), p=0.33, I^2=0%. [moderate vs higher CHO diet (6m) not reported because 1 RCT with T1D] • Results from sensitivity analyses by Sainsbury (3 and 6 m) after exclusion of RCTs at high risk of bias, in agreement with main analyses. • Results from sensitivity analyses by Sainsbury (3m) after exclusion of RCTs with greater weight, disagreed with main analysis: -0.05 (-0.17, 0.06), p=0.35, I^2=0%. Heterogeneity • Sainsbury at 3m, I^2=28%; at 6m, I^2=44% Overlap 0 RCTs in all 3 MAs; Korsmo-Haugen: 3/6 RCTs in Sainsbury; van Zuuren: 1/7 RCTs in Sainsbury, 0/7 RCTs in Korsmo-Haugen.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 3m: 9/12 RCTs were either at unclear or high risk of bias. 6m: 7/10 RCTs were either at unclear or high risk of bias Analysis Sainsbury at 3 m, ITT in 33% of RCTs (including 2 RCTs that did not report type of analysis); at 6 m, ITT in 70% of RCTs.
Comments	
Difference in effect/Overall grade	**Significantly greater reduction in the lower CHO group/Adequate**

Table A16.2B: HbA1c, longer term (≥12 m)

MA with largest number of RCTs/sample size	Sainsbury: (12 RCTs, n=1403)
Results of MA (mean difference in change, %)	No difference in effect between lower and higher CHO groups. -0.09 (-0.21, 0.03), p=0.12
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Agreed with results of 2nd largest MA, Korsmo-Haugen (10 RCTs, 1030 participants) (no difference in effect): 0.00 (-0.10, 0.09), p=NR • Disagreed with results from 2 smaller MAs (significantly greater reduction in HbA1c in lower CHO group): Huntriss (7 RCTs, n=645) -0.28 (-0.53, -0.02), p=0.03; van Zuuren (4 RCTs, n=390) -0.36 (-0.58, -0.14), p=0.001 • Disagreed with results from sensitivity analysis by Sainsbury; after exclusion of RCTs at high risk of bias, significantly greater reduction in HbA1c with the lower CHO diet: -0.13 (-0.26, -0.01), p=NR; however, separate subgroup analyses by CHO quantity (lower vs higher and moderate vs higher) showed no difference in effect. <u>Heterogeneity</u> • Sainsbury, I^2=16%; Korsmo-Haugen, I^2=0%; Huntriss, I^2=54%, van Zuuren, I^2=0%. <u>Overlap</u> 8 RCTs in both Korsmo-Haugen and Sainsbury; 2 RCTs in all 4 MAs; 2 RCTs in Korsmo-Haugen, Sainsbury, van Zuuren; in van Zuuren, 4/4 RCTs in both Korsmo-Haugen and Sainsbury; in Huntriss, 4/7 RCTs in Korsmo-Haugen, 4/7 RCTs in Sainsbury.
Quality (risk of bias, type of analysis). Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> 5/12 RCTs in Sainsbury were either at unclear or high risk of bias. Risk of bias was not reported for 2 RCTs. <u>Analysis</u> Sainsbury, ITT in 58% of RCTs.
Comments	Agreement between 2 largest MAs (Sainsbury and Korsmo-Haugen) Disagreement between Sainsbury main analysis and sensitivity analysis (removal of 1 RCT at high risk of bias)
Difference in effect/Overall grade	**Inconsistent**

Table A16.3A: Fasting plasma glucose, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	Only 1 MA (van Zuuren) reported on fasting plasma glucose (6 RCTs, n=396).
Results of MA (mean difference in change, %)	Significantly greater reduction in the lower CHO group: -0.51 (-0.91, -0.12), p=0.01
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from sensitivity analyses in agreement with the main results. Heterogeneity • I^2=71% Overlap N/A
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 6/6 RCTs were either at unclear or serious risk of bias. Analysis ITT in 67% of RCTs.
Comments	Only 1 MA of 6 RCTs with 396 participants; includes 1 non-randomised trial (Nielsen, n=31) reported as at 'serious' risk of bias. Van Zuuren included only RCTs that compared low CHO diets specifically with low fat (≤30% TE intake).
Difference in effect/Overall grade	**Significantly greater reduction in the lower CHO group/Moderate**

Table A16.3B: Fasting plasma glucose, longer term (≥12 m)

MA with largest number of RCTs/sample size	Only 1 MA (van Zuuren) reported on fasting plasma glucose (4 RCTs, n=340).
Results of MA (mean difference in change, %)	No difference in effect between lower and higher CHO groups: -0.37 (-1.22, 0.48), p=0.39
Agreement with results from other MAs, additional sub-group and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results of sensitivity analysis excluding studies at high risk of bias (1 RCT), in agreement with main results. • Disagreement with the results of a fixed-effects model but unclear why fixed-effects model used because of high heterogeneity (main analysis=random-effects model). Heterogeneity • I^2=92% Overlap N/A
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 4/4 RCTs were either at unclear or high risk of bias. Analysis ITT in 50% of RCTs.
Comments	Downgraded because only 1 MA of 4 RCTs (n=340) with very high heterogeneity (92%) and which included a non-randomised study (Nielson, n=31) reported at 'serious' risk of bias.
Difference in effect/Overall grade	**Insufficient**

Table A16.4A: Serum total cholesterol, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	Only 1 MA (Korsmo-Haugen) reported on serum total cholesterol (4 RCTs, n=279).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher CHO groups: Korsmo-Haugen: -0.06 (-0.41, 0.30), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement N/A Heterogeneity I^2=57%. Overlap N/A
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 4/4 RCTs were either at unclear or high risk of bias. Analysis ITT in 75% of RCTs.
Comments	Only 1 MA with very small sample size (n=279).
Difference in effect/Overall grade	**No difference in effect/Moderate**

Table A16.4B: Serum total cholesterol, longer term (≥12 m)

MA with largest number of RCTs/sample size	Korsmo-Haugen (10 RCTs, n=1094).
Results of MA (mean difference in change, mmmol/L)	No difference in effect between lower and higher CHO groups: 0.07 (-0.04, 0.19), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from Huntriss in agreement (no difference in effect). Heterogeneity • I^2=23% Overlap 4 RCTs in both.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias 7/10 RCTs were either at unclear or high risk of bias. Analysis ITT in 60% of RCTs (including 1 RCT that did not report type of analysis).
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A16.5A: Serum triacylglycerol, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	van Zuuren (6 RCTs, n=508).
Results of MA (mean difference in change, mmol/L)	Significantly greater reduction in serum triacylglycerol with the LCD: -0.22 (-0.37, -0.08), p=0.002
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Consistent with results from Korsmo-Haugen (7 RCTs, n=424): -0.18 (-0.36, 0.00), p=NR. **Note**: upper CI=0 and publication did not report significance. <u>Heterogeneity</u> • van Zuuren, I^2=41%; Korsmo-Haugen, I^2=20%. <u>Overlap</u> 1 RCT in both MAs (Yamada, 2014).
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> van Zuuren: unclear in 6/6 RCTs; Korsmo-Haugen: unclear or high in 7/7 RCTs. <u>Analysis</u> van Zuuren, ITT in 67% of RCTs; Korsmo-Haugen, ITT in 57% of RCTs.
Comments	Although agreement between the 2 MAs, Korsmo-Haugen did not report significance (upper CI=0).
Difference in effect/Overall grade	**Significantly greater reduction in the lower CHO group/Adequate**

Table A16.5B: Serum triacylglycerol, longer term (≥12 m)

MA with largest number of RCTs/sample size	Korsmo-Haugen (9 RCTs, n=967).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher CHO groups: -0.10 (-0.23, 0.03), p=NR, I^2=61%
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Disagreed with results of other MAs which reported significantly greater reduction in lower CHO group: Huntriss (7 RCTs, n=645): -0.24 (-0.35, -0.13), p<0.0001 van Zuuren (5 RCTs; n=468):-0.25 (-0.47, -0.04), p=0.02 <u>Heterogeneity</u> • Korsmo-Haugen, I^2=61%; Huntriss, I^2=0%; van Zuuren, I^2=73%. <u>Overlap</u> 2 RCTs in all 3 MAs; Korsmo-Haugen and Huntriss: 4 (4/7 RCTs in Huntriss, included in Korsmo-Haugen); Korsmo-Haugen and van Zuuren: 4 (4/5 RCTs in van Zuuren, included in Korsmo-Haugen); Huntriss and van Zuuren: 2 RCTs.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> Korsmo-Haugen: unclear in 6/9 RCTs, low in 3/9 RCT; van Zuuren, high or unclear in 5/5 RCTs. <u>Analysis</u> Korsmo-Haugen, ITT in 67% of RCTs; Huntriss, ITT in 71% RCTs (including 1 RCT that did not report type of analysis); van Zuuren, ITT in 60% of RCTs.
Comments	Downgraded because MAs did not agree. Huntriss, only MA to include RCT by Esposito (carried 62% weight in MA).
Difference in effect/Overall grade	**Inconsistent**

Table A16.6A: Serum LDL cholesterol, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	van Zuuren (5 RCTs, n=372).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher CHO groups: -0.02 (-0.09, 0.13), p=0.75
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from Korsmo-Haugen in agreement (6 RCTs, n=345): -0.08 (-0.29, 0.14), p=NR. Heterogeneity • van Zuuren, I^2=0%; Korsmo-Haugen, I^2=50%. Overlap 1 RCT in both MAs.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias van Zuuren: unclear in 5/5 RCTs; Korsmo-Haugen: unclear or high in 6/6 RCTs. Analysis van Zuuren, ITT in 80% of RCTs; Korsmo-Haugen, ITT in 67% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A16.6B: Serum LDL cholesterol, longer term (≥12 m)

MA with largest number of RCTs/sample size	Korsmo-Haugen (9 RCTs, n=1064).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher CHO groups: 0.03 (-0.10, 0.16), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	Agreement • Results from 2 other MAs in agreement (no difference in effect): Huntriss (5 RCTs, n=389): 0.05 (-0.10, 0.19), p=0.54 van Zuuren 4 RCTs, n=375: -0.07 (-0.23, 0.09), p=0.41 Heterogeneity • Korsmo-Haugen, I^2=51%. Overlap 2 RCTs in all MAs.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	Risk of bias Korsmo-Haugen: unclear or high in 6/9 RCTs. Analysis Korsmo-Haugen, ITT in 56% of RCTs.
Comments	
Difference in effect/Overall grade	**No difference in effect/Adequate**

Table A16.7A: Serum HDL cholesterol, shorter term (≥3 to 6 m)

MA with largest number of RCTs/sample size	van Zuuren (6 RCTs, n=508).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher CHO groups: 0.09 (-0.03, 0.22), p=0.13
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Results from Korsmo-Haugen (6 RCTs, n=345) in agreement (no difference in effect): -0.01 (-0.07, 0.04), p=NR. • Results from a sensitivity analysis by van Zuuren excluding RCTs causing substantial heterogeneity disagreed with the main results (significantly greater increase): 0.17 (0.11, 0.23), p<0.00001, I^2=0%. <u>Heterogeneity</u> • van Zuuren main analysis, I^2=91%; Korsmo-Haugen, I^2=15%. <u>Overlap</u> 1 RCT in both MAs.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> van Zuuren, unclear in 6/6 RCTs; Korsmo-Haugen: unclear or high in 6/6 RCTs. <u>Analysis</u> van Zuuren, ITT in 67% of RCTs; Korsmo-Haugen, ITT in 67% of RCTs.
Comments	Downgraded because of disagreement with sensitivity analysis and high heterogeneity in largest MA (91%).
Difference in effect/Overall grade	**Inconsistent**

Table A16.7B: Serum HDL cholesterol, longer term (≥12 m)

MA with largest number of RCTs/sample size	Korsmo-Haugen (10 RCTs, n=1093).
Results of MA (mean difference in change, mmol/L)	No difference in effect between lower and higher CHO groups: 0.06 (-0.01, 0.13), p=NR
Agreement with results from other MAs, additional subgroup and/or sensitivity analyses Consider: • statistical significance (p-values and CI) • direction and magnitude of the effect size • heterogeneity • overlap of RCTs in MAs	<u>Agreement</u> • Results from the 2 other MAs disagreed (significantly greater increase): Huntriss (7 RCTs, n=645): 0.06 (0.04, 0.09), p<0.00001 van Zuuren (4 RCTs, n=375): 0.11 (0.05, 0.18), p<0.0007; <u>Heterogeneity</u> • Korsmo-Haugen, I^2=71%, Huntriss, I^2=1%, van Zuuren, I^2=66%. <u>Overlap</u> 2 RCTs in all MAs; van Zuuren: 4/4 RCTs in Korsmo-Haugen; Huntriss: 4/7 RCTs in Korsmo-Haugen.
Quality (risk of bias, type of analysis) Consider: • RCTs within each MA • risk of bias (assessed by publication author)	<u>Risk of bias</u> Korsmo-Haugen: unclear or high in 7/10 RCTs; van Zuuren: unclear or high in 4/4 RCTs. <u>Analysis</u> Korsmo-Haugen, ITT in 60% of RCTs; Huntriss, ITT in 71% of RCTs (including 1 RCT that did not report type of analysis); van Zuuren, ITT in 50% of RCTs.
Comments	Downgraded because of disagreement between largest MA (10 RCTs, n=1093) and the 2 smaller MAs All 4 RCTs in smallest MA (van Zuuren) also in largest MA. 1 RCT (Esposito) weighted 73% in Huntriss MA.
Difference in effect/Overall grade	**Inconsistent**

Annex 17: Within-group analyses for primary and secondary outcomes in prioritised systematic reviews with meta-analyses

1. Out of the 4 prioritised SRs, only Sainsbury et al (2018) conducted MAs of within group changes for the outcome of HbA1c only and the results of these MAs are reported below (see paragraphs 2 to 6). The other 3 SRs did not conduct MAs of within-group changes for any outcomes. Narrative summaries of within group changes in the primary publications that were included in MAs for all the other outcomes (body weight, fasting plasma glucose, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol) are provided in paragraphs 7 to 20 and the results are summarised in Tables A17.1 to A17.8.

HbA1c

2. Sainsbury et al (2018) conducted separate MAs of within-group analyses in HbA1c at 3, 6, 12 and 24 months.
3. Shorter-term studies (3 months): There were significant reductions in HbA1c within both lower (weighted mean within-group change: -0.77%, 95% CI -1.15 to -0.40, p=NR; I^2=NR, type of statistical model NR; 10 RCTs, NR participants), and higher carbohydrate groups (weighted mean within-group change: -0.50%, 95% CI -0.77 to -0.22, p=NR; I^2=NR, type of statistical model NR; 10 RCTs, NR participants).
4. Shorter-term studies (6 months): There were significant reductions in HbA1c within both lower (weighted mean within-group change: -0.52%, 95% CI -0.82 to -0.21, p=NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants) and higher carbohydrate groups (weighted mean within-group change: -0.28%, 95% CI -0.51 to -0.05, p=NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants).
5. Longer-term studies (≥12 months): There were non-significant reductions in HbA1c within both lower (weighted mean within-group change: -0.43%, 95% CI -0.98 to 0.02, p-value NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants) and higher carbohydrate groups (weighted mean within-group change: -0.21%, 95% CI -0.76 to 0.34, p=NR; I^2=NR, type of statistical model NR; 11 RCTs, NR participants).
6. Longer-term studies (≥24 months): There were non-significant reductions in HbA1c within both lower (weighted mean within-group change: -0.29%, 95% CI -1.07 to 0.49, p-value NR; I^2=NR, type of statistical model NR; 3 RCTs, NR participants) and higher carbohydrate groups (weighted mean within-group change: -0.05%, 95% CI -0.51 to 0.41, p-value NR; I^2=NR, type of statistical model NR; 3 RCTs, NR participants.

Body weight

7. Shorter-term studies (3 months) (12 RCTs): 3 RCTs reported significant reductions in body weight within both lower (range, -3.1 to -5.9 kg) and higher (range, -1.0 to -5.1 kg) carbohydrate groups; 9 did not report within-group analyses (Table A17.1).
8. Shorter-term studies (>3 to 6 months) (17 RCTs): 5 RCTs reported significant reductions in body weight within both lower (range, -2.1 to -11.1 kg) and higher (range, -1.0 to -7.0 kg) carbohydrate groups; 1 reported a significant reduction within the lower carbohydrate group only (-14.7 kg); 1 reported non-significant reductions in body weight within both groups; 10 did not report within-group analyses (Table A17.2).
9. Longer-term studies (≥12 months) (16 publications): 5 RCTs reported a significant reduction in average body weight in both the lower (range, -1.9 to -3.8 kg) and higher (range, -2.1 to -5.4 kg) carbohydrate groups; 1 reported non-significant reductions in both groups; 10 did not report within-group changes (Table A17.3).

Fasting plasma glucose

10. Shorter-term studies (≥3 to 6 months) (6 RCTs): 1 RCT reported a significant reduction in fasting plasma glucose within the lower carbohydrate group only (-1.6 mmol/L); 1 reported non-significant changes within both groups; 3 did not report within-group analyses (Table A17.4).
11. Longer-term studies (≥12 months) (4 RCTs): 1 RCT reported significant reductions in fasting plasma glucose in both lower (-3.4 mmol/L) and higher carbohydrate groups (-4.9 mmol/L); 3 did not report within-group analyses (Table A17.4).
12. One RCT (Shai et al, 2008) reported only 14% of participants with T2D, so data were not included here.

Serum total cholesterol

13. Shorter-term studies (≥3 to 6 months) (4 RCTs): 1 RCT reported a significant reduction in serum total cholesterol within the lower carbohydrate group only (-0.3 mmol/L); 3 reported non-significant changes in serum total cholesterol within both groups (Table A17.5).
14. Longer-term studies (≥12 months) (12 RCTs): 7 RCTs reported non-significant changes in serum total cholesterol within both groups; 6 did not report within-group analyses (Table A17.5).

Serum triacylglycerol

15. Shorter-term studies (≥3 to 6 months) (12 RCTs): 4 RCTs reported significant reductions in serum triacylglycerol within lower carbohydrate groups only (range, --0.15 to -0.76 mmol/L); 1 reported significant reductions within both lower (-0.52

mmol/L) and higher (-0.55 mmol/L) carbohydrate groups; 2 reported non-significant changes within both groups; 4 did not report within-group analyses (Table A17.6).

16. Longer-term studies (≥12 months) (13 RCTs): 7 RCTs reported non-significant changes within both groups; 6 did not report within-group analyses (Table A17.6).

Serum LDL cholesterol

17. Shorter-term studies (≥3 to 6 months) (10 RCTs): 1 RCT reported significant reductions in serum LDL cholesterol within the lower carbohydrate group only (-0.20 mmol/L); 7 reported non-significant reductions within both groups; 2 did not report within-group analyses (Table A17.7).

18. Longer-term studies (≥12 months) (12 RCTs): 1 RCT reported significant reductions in serum LDL cholesterol within both lower (-0.30 mmol/L) and higher (-0.30 mmol/L) carbohydrate groups (at 24 months); 5 reported non-significant reductions within both groups; and 5 did not report within-group analyses (Table A17.7).

Serum HDL cholesterol

19. Shorter-term studies (≥3 to 6 months) (11 RCTs): 1 RCT reported a significant increase in serum HDL cholesterol within both the lower (0.12 mmol/L) and higher (0.01 mmol/L) carbohydrate groups; 2 reported significant increases within lower carbohydrate groups only (0.10 and 0.15 mmol/L); 1 reported a significant reduction within the lower carbohydrate group only (-0.03 mmol/L); 4 reported non-significant changes within both groups; 3 did not report within-group analyses (Table A17.8).

20. Longer-term studies (≥12 months) (13 RCTs): 2 RCTs reported significant increases in serum HDL cholesterol within both lower (range, 0.11 to 0.23 mmol/L) and higher (range, 0.08 to 0.15 mmol/L) carbohydrate groups; 1 reported a significant increase in the lower carbohydrate group only (0.23 mmol/L); 3 reported non-significant changes within both groups; 7 did not report within-group analyses (Table A17.8).

Table A17.1: Within-group changes in body weight (3 m)

Primary publication, lead author (year)	Timepoint	Lower carbohydrate (LC) group	Higher carbohydrate (HC) group	Within-group difference (reported statistics only)
		Mean weight reduction in each group, kg		
Brehm (2009)	4 m	-4.5	-3.9	NR
Brunerova (2007)	3 m	-5.9	-5.1	p<0.01
Daly (2006)	3 m	-3.6	-0.9	NR
Davis (2009)	3 m	-5.2	-3.2	NR
Larsen (2011)	3 m	-2.8	-3.1	NR
Luger (2013)	3 m	-3.1	-1.0	LC: p=0.000; HC: p=0.03
Parker (2002)	3 m	-5.5	-4.8	NR
Saslow (2014)	3 m	-5.5	-2.6	LC: p<0.01; HC: p<0.05
Watson (2016)	3 m	-8.0	-7.6	NR
Westman (2008)	3 m	-8.3	-4.2	NR
Wolever (2008)	3 m	NR	NR	NR
Wycherley (2010)	4 m	NR	NR	NR

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean weight reduction, kg (range, smallest to largest reduction)		
Sainsbury (2018), based on 9 out of 12 RCTs, which provided data at 3 months; 953 participants	3 m	-5.3 (-2.8 to -8.3)	-3.6 (-0.9 to -7.6)	3 RCTs: significant reduction in weight within both groups 9 RCTs: did not report within-group statistical analysis

Table A17.2: Within-group changes in body weight (≥3 to 6 m)

Primary publication, lead author (year)	Timepoint	LC group	HC group	Within-group difference (reported statistics only)
		Mean weight reduction in each group, kg		
Brehm (2009)	8 m	-4.5	-3.9	NR
Daly (2006)	3 m	-3.6	-0.9	NR
Davis (2009)	6 m	-4.8	-4.4	NR
de Bont (1981)	6 m	-0.9	-2.7	NR
Goday (2016)	4 m	-14.7	-5.1	LC: p<0.0001
Guldbrand (2012)	6 m	-3.9	-4.6	p<0.001
Jenkins (2014)	3 m	-2.1	-1.6	p<0.05
Jonasson (2014)	6 m	NR	NR	NR
Krebs (2012)	6 m	-3.2	-3.2	NR
Luger (2013)	3 m	-3.1	-1.0	LC: p=0.000; HC: p=0.03
McLaughlin (2007)	4 m	-5.9	-7.0	p<0.001
Nielsen (2005)	6 m	-11.4	-1.8	NR
Tay (2014)	6 m	-12.0	-11.5	NR
Watson (2016)	6 m	-8.9	-7.7	NR
Westman (2008)	6 m	-11.1	-6.9	p<0.05
Wolever (2008)	6 m	NR	NR	NR
Yamada (2014)	6 m	-2.6	-1.4	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean weight reduction, kg (range, smallest to largest reduction)		
Sainsbury (2018), based on 8 out of 9 RCTs (Strychar et al, 2009 excluded because study of patients with T1D), 1484 participants	6 m	-5.8 (-2.6 to -11.1)	-4.7 (-1.4 to -7.7)	2 RCTs: significant reduction in weight within both groups 1 RCT: non-significant reduction in weight within both groups 5 RCTs: did not report within-group statistical analysis
van Zuuren (2018), 7 RCTs, 537 participants	4 to 6 m	-7.2 (-0.9 to -14.7)	-4.5 (-1.4 to -11.5)	1 RCT: significant reduction in weight within both groups 1 RCT: significant reduction in weight within LC group only 1 RCT: non-significant reduction in weight within both groups 4 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 7 RCTs, 424 participants	3 to 6 m	-4.7 (-2.1 to -11.1)	-3.1 (-0.9 to -7.0)	4 RCTs: significant reduction in weight within both groups 1 RCT: non-significant reduction in weight within both groups 2 RCTs: did not report within-group statistical analysis

Table A17.3: Within-group changes in body weight (≥12 m)

Primary publication, lead author (year)	LC group	HC group	Within-group difference (reported statistics only)
	Mean weight change in each group, kg		
Brehm (2009)	-4.0	-3.8	NR
Brinkworth (2004)	-3.8	-2.1	p<0.01
Davis (2009)	-3.1	-3.1	NR
Elhayany (2010)	-8.9	-7.4	NR
Esposito (2009)	-6.2	-4.2	NR
Facchini (2003)	-2.0	-1.0	non-significant
Goldstein (2011)	-3.4	-5.4	p<0.001
Guldbrand (2012)	-1.9	-3.9	p<0.001
Guldbrand (2012)	-2.0	-2.9	LC: p=0.02; HC: p=0.002
Hockaday (1978)	-3.8	-4.6	p<0.001
Krebs (2012)	-3.2	-2.4	NR
Larsen (2011)	-2.2	-2.2	NR
Mayer (2014)	-7.5	-8.1	NR
Pedersen (2014)	-7.8	-5.7	NR
Tay (2015)	-9.8	-10.1	NR
Wolever (2008)	-0.4	2.8	NR

SR with MA, lead author (year), number of RCTs and participants	LC group	HC group	Summary of within-group difference
	Mean weight change, kg (range, smallest to largest reduction)		
Korsmo-Haugen (2018) 10 RCTs, 1163 participants	-3.8 (-0.4 to -8.9)	-3.3 (-7.6 to 2.8)	6 RCTs: significant reduction in weight within both groups 1 RCT: non-significant reduction in weight within both groups 1 RCT: did not report within-group analysis
Sainsbury (2018) 10 RCTs, 1484 participants	-4.5 (-0.4 to -9.8)	-3.8 (-10.1 to 2.8)	2 RCTs: significant reduction in weight within both groups 8 RCTs: did not report within-group analysis
van Zuuren (2018) 5 RCTs, 483 participants	-3.6 (-0.4 to -8.9)	-3.2 (-7.4 to 2.8)	2 RCTs: significant reduction in weight within both groups 3 RCT: did not report within-group analysis
Huntriss (2018) 6 RCTs, 567 participants	-4.1 (-7.5 to -1.9)	-4.5 (-8.1 to -2.2)	2 RCTs: significant reduction in weight within both groups 4 RCTs: did not report within-group analysis

Table A17.4: Within-group changes in fasting plasma glucose

Primary publication, lead author (year)	Timepoint	LC group	HC group	Within-group difference (reported statistics only)
		Mean change in fasting plasma glucose, mmol/L		
de Bont (1981)	6 m	-0.50	-0.30	NR
Elhayany (2010)	12 m	-4.29	-3.50	NR
Goday (2016)	4 m	-1.55	-0.95	LC: p<0.0001
Hockaday (1978)	12 m	-3.40	-4.90	p<0.001
Nielsen (2005)	6 m	-3.40	-0.60	NR
Shai (2008)1	6 m/12 m	Data excluded as only 14% of study population had type T2D.		
Tay (2014)	6 m	-1.10	-1.60	NR
Wolever (2008)	12 m	NR	NR	NR
Yamada (2014)	6 m	-0.78	0.44	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean change in fasting plasma glucose, mmol/L (range)		
van Zuuren (2018) based on 5 out of 6 RCTs (Shai et al, 2008 excluded because only 14% of study participants with T1D), 396 participants	4 to 6 m	-1.47 (-3.40 to -0.50)	-0.60 (-1.60 to 0.44)	1 RCT: significant reduction in FBG within LC group only 1 RCT: non-significant changes in FBG within both groups 3 RCTs: did not report within-group statistical analysis
van Zuuren (2018) based on 3 out of 4 RCTs (Shai et al, 2008 excluded because only 14% of study participants with T1D), 340 participants	≥12 m	-3.85 (-4.29 to -3.40)	-4.20 (-4.90 to -3.50)	1 RCT: significant reduction in FBG within both groups 2 RCTs: did not report within-group statistical analysis

Table A17.5: Within-group changes in serum total cholesterol

Primary publication, lead author (year)	Timepoint	LC group	HC group	Within-group difference (reported statistics only)
		Mean change in serum total cholesterol, mmol/L		
Brinkworth (2004)	16 m	0.08	0.35	non-significant
Davis (2009)	12 m	0.10	-0.13	NR
Elhayany (2010)	12 m	-0.88	-0.96	NR
Esposito (2009)	12 m	-0.39	-0.15	NR
Facchini (2003)	48 m	0.30	-0.20	non-significant
Goldstein (2011)	12 m	-0.21	-0.05	non-significant
Guldbrand (2012)	12 m	0.20	0.00	non-significant
Guldbrand (2012)	24 m	-0.10	-0.30	non-significant
Jenkins (2014)	3 m	-0.30	0.04	LC: $p<0.05$
Jonasson (2014)	6 m	-0.10	-0.10	non-significant
Krebs (2012)	24 m	-0.24	-0.17	non-significant
Larsen (2011)	12 m	-0.15	0.01	NR
Mayer (2014)	11 m	-0.05	-0.28	NR
McLaughlin (2007)	4 m	-0.18	-0.05	non-significant
Pedersen (2014)	12 m	0.00	-0.10	non-significant
Tay (2015)	12 m	-0.10	-0.10	NR
Westman (2008)	6 m	-0.11	-0.15	non-significant
Wolever (2008)	12 m	-0.02	-0.05	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean change in serum total cholesterol, mmol/L (range)		
Korsmo-Haugen (2018) 4 RCTs, 279 participants	3 to 6 m	-0.17 (-0.30 to -0.10)	-0.07 (-0.15 to 0.04)	1 RCT: significant reduction in serum total cholesterol within LC group only 3 RCTs: non-significant changes in serum total cholesterol within both groups
Korsmo-Haugen (2018) 10 RCTs, 1094 participants	≥12 m	-0.11 (-0.88 to 0.30)	-0.16 (-0.96 to 0.35)	7 RCTs: non-significant changes in serum total cholesterol within both groups 3 RCTs: did not report within-group statistical analysis
Huntriss (2018) 7 RCTs, 645 participants	12 m	-0.14 (-0.39 to 0.10)	-0.10 (-0.28 to -0.01)	2 RCTs: non-significant changes in serum total cholesterol within both groups 5 RCTs: did not report within-group statistical analysis

Table A17.6: Within-group changes in serum triacylglycerol

Primary publication, lead author (year)	Timepoint	LC group	HC group	Within-group difference (reported statistics only)
		Mean change in serum triacylglycerol, mmol/L		
Brinkworth (2004)	64 w	0.06	-0.13	non-significant
Daly (2006)	3 m	-0.67	-0.25	NR
Davis (2009)	6 m	-0.02	0.04	NR
Davis (2009)	12 m	-0.15	-0.01	NR
De Bont (1981)	6 m	-0.11	-0.03	NR
Elhayany (2010)	12 m	-1.52	-1.46	NR
Esposito (2009)	12 m	-0.44	-0.22	NR
Goday (2016)	6 m	-0.41	0.20	LC: p=0.004
Goldstein (2011)	12 m	-0.45	-0.05	non-significant
Guldbrand (2012)	6 m	-0.20	0.00	non-significant
Guldbrand (2012)	12 m	-0.30	-0.10	non-significant
Guldbrand (2012)	24 m	-0.20	-0.10	non-significant
Hockaday (1978)	12 m	-0.10	0.00	non-significant
Jenkins (2014)	3 m	-0.15	-0.01	LC: p<0.05
Jonasson (2014)	6 m	-0.20	0.00	non-significant
Krebs (2012)	24 m	-0.04	-0.01	non-significant
Larsen (2011)	12 m	-0.47	-0.30	NR
Luger (2013)	3 m	-0.57	-0.15	p=0.01
Mayer (2014)	12 m	-0.4	-0.10	NR
McLaughlin (2007)	4 m	-0.52	-0.55	LC: p=0.008; HC: p=0.007
Pedersen (2014)	12 m	-0.6	-0.30	NR
Tay (2014)	6 m	-0.50	-0.10	NR
Tay (2015)	12 m	-0.4	-0.01	NR
Westman (2008)	6 m	-0.76	-0.22	LC: p<0.05
Wolever (2008)	12 m	0.14	0.30	non-significant
Yamada (2014)	6 m	-0.66	-0.08	LC: p=0.02

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean change in serum triacylglycerol, mmol/L (range)		
Korsmo-Haugen (2018), 7 RCTs, 424 participants	3 to 6 m	-0.50 (-0.76 to -0.15)	-0.18 (-0.55 to 0.00)	4 RCTs: significant reduction in serum triacylglycerol within LC group only 1 RCT: significant reduction in serum triacylglycerol within both groups 1 RCT: non-significant changes within both groups 1 RCT: did not report within-group statistical analysis
van Zuuren (2018), 6 RCTs, 508 participants	4 to 6 m	-0.32 (-0.66 to -0.02)	-0.06 (-0.20 to 0.04)	1 RCT: significant reduction in serum triacylglycerol within LC group only 2 RCTs: non-significant changes within both groups 3 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 9 RCTs, 967 participants	≥12 m	-0.36 (-1.52 to 0.14)	-0.23 (-1.46 to 0.30)	5 RCTs: non-significant changes in serum triacylglycerol within both groups 4 RCTs: did not report within-group statistical analysis
Huntriss (2018), 7 RCTs, 645 participants	12 m	-0.37 (-0.47 to -0.15)	-0.12 (-0.30 to -0.01)	2 RCTs: non-significant changes in serum triacylglycerol within both groups 5 RCTs: did not report within-group statistical analysis
van Zuuren (2018), 5 RCTs, 468 participants	≥12 m	-0.39 (-1.52 to 0.14)	-0.14 (-0.88 to 0.30)	3 RCTs: no significant change within both groups 2 RCT: did not report within-group statistical analysis

Table A17.7: Within-group changes in serum LDL cholesterol

Primary publication, lead author (year)	Timepoint	LC group	HC group	Within-group difference (reported statistics only)
		Mean change in serum LDL cholesterol, mmol/L		
Brinkworth (2004)	16	-0.19	0.27	non-significant
Davis (2009)	6	-0.10	-0.25	NR
Davis (2009)	12	-0.04	-0.18	NR
Elhayany (2010)	12	-0.61	-0.37	NR
Facchini (2003)	48	0.07	-0.12	non-significant
Goday (2016)	4	-0.05	-0.07	non-significant
Guldbrand (2012)	6	-0.20	-0.10	non-significant
Guldbrand (2012)	12	-0.20	-0.10	non-significant
Guldbrand (2012)	24	-0.30	-0.30	LC: p=0.02; HC: p=0.017
Jenkins (2014)	3	-0.20	0.04	LC: p<0.05
Jonasson (2014)	6	-0.20	-0.10	non-significant
Krebs (2012)	24	-0.17	-0.20	non-significant
Larsen (2011)	12	-0.05	0.04	NR
Luger (2013)	3	-0.11	-0.13	non-significant
Mayer (2014)	12	-0.02	-0.27	NR
McLaughlin (2007)	4	-0.13	0.00	non-significant
Pedersen (2014)	12	0.10	0.00	non-significant
Tay (2014)	6	-0.30	-0.30	NR
Tay (2015)	13	-0.10	-0.20	NR
Westman (2008)	6	0.03	-0.07	non-significant
Wolever (2008)	12	-0.13	-0.10	non-significant
Yamada (2014)	6	-0.12	-0.04	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean change in serum LDL cholesterol, mmol/L (range)		
van Zuuren (2018), 5 RCTs, 372 participants	4 to 6 m	-0.15 (-0.30 to -0.05)	-0.15 (-0.30 to -0.04)	3 RCTs: non-significant reductions in serum LDL cholesterol within both groups 2 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 6 RCTs, 345 participants	3 to 6 m	-0.12 (-0.20 to 0.03)	-0.05 (-0.13 to 0.04)	1 RCT: significant reduction in serum LDL cholesterol within LC group only 5 RCTs: non-significant change within both groups
van Zuuren (2018), 4 RCTs, 375 participants	≥12 m	-0.25 (-0.61 to -0.04)	-0.19 (-0.37 to -0.10)	1 RCT: non-significant changes in serum LDL cholesterol within both groups 3 RCTs: did not report within-group statistical analysis
Huntriss (2018), 5 RCTs, 389 participants	>12 m	-0.08 (-0.20 to -0.02)	-0.14 (-0.27 to 0.04)	2 RCTs: non-significant changes in serum LDL cholesterol in both arms 3 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 9 RCTs, 1064 participants	>12 m	-0.15 (-0.61 to 0.10)	-0.11 (-0.37 to 0.27)	1 RCT: significant reductions in serum LDL cholesterol within both groups 5 RCTs: non-significant changes within both groups 3 RCTs: did not report within-group statistical analysis

Table A17.8: Within-group changes in serum HDL cholesterol

Primary publication, lead author (year)	Timepoint	LC group	HC group	Within-group difference (reported statistics only)
		Mean change in serum HDL cholesterol, mmol/L		
Brinkworth (2004)	16 m	0.16	0.15	p<0.001
Davis (2009)	6 m	0.16	-0.01	NR
Davis (2009)	12 m	0.16	0.06	NR
de Bont (1981)	6 m	-0.19	-0.09	NR
Elhayany (2010)	12 m	0.13	-0.05	NR
Esposito (2009)	12 m	0.10	0.03	NR
Facchini (2003)	48 m	0.23	-0.05	LC: p<0.05
Goday (2016)	4 m	-0.04	-0.07	non-significant
Goldstein (2011)	12 m	0.11	0.14	non-significant
Guldbrand (2012)	6 m	0.12	0.01	LC: p<0.001, HC: p=0.002
Guldbrand (2012)	12 m	0.11	0.08	LC: p=0.024; HC: p=0.004
Guldbrand (2012)	24 m	0.23	0.11	LC: p<0.001; HC: p=0.002
Jenkins (2014)	3 m	-0.03	0.00	LC: p<0.05
Jonasson (2014)	6 m	0.10	0.00	LC: p<0.05
Krebs (2012)	24 m	-0.01	0.02	non-significant
Larsen (2011)	12 m	0.08	0.08	NR
Luger (2013)	3 m	0.02	0.04	non-significant
Mayer (2014)	12 m	0.07	0.03	NR
McLaughlin (2007)	4 m	0.05	0.05	non-significant
Pedersen (2014)	12 m	0.10	0.10	NR
Tay (2014)	6 m	0.20	0.05	NR
Tay (2015)	13 m	0.10	0.06	NR
Westman (2008)	6 m	0.15	0.00	LC: p<0.05
Wolever (2008)	12 m	0.05	-0.05	non-significant
Yamada (2014)	6 m	0.14	-0.11	non-significant

SR with MA, lead author (year), number of RCTs and participants	Timepoint	LC group	HC group	Summary of within-group difference
		Mean change in serum HDL cholesterol, mmol/L (range)		
van Zuuren (2018), 6 RCTs, 508 participants	4 to 6 m	0.07 (-0.19 to 0.20)	-0.04 (-0.11 to 0.05)	1 RCT: significant increases in serum HDL cholesterol within both groups 2 RCTs: non-significant changes within both groups 3 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 6 RCTs, 345 participants	3 to 6 m	0.07 (-0.03 to 0.15)	0.00 (-0.11 to 0.05)	3 RCTs: significant change in HDL cholesterol within LC group only 3 RCTs: non-significant changes within both groups
van Zuuren (2018), 4 RCTs, 375 participants	≥12 m	0.11 (0.05 to 0.16)	0.01 (-0.05 to 0.08)	1 RCT: significant increases in serum HDL cholesterol within both groups 1 RCT: non-significant changes within both groups 2 RCTs: did not report within-group statistical analysis
Huntriss (2018), 7 RCTs, 645 participants	>12 m	0.10 (0.07 to 0.16)	0.07 (0.03 to 0.14)	1 RCT: significant increases in serum HDL cholesterol within both groups 1 RCT: non-significant changes within both groups 5 RCTs: did not report within-group statistical analysis
Korsmo-Haugen (2018), 10 RCTs, 1093 participants	>12 m	0.12 (-0.01 to 0.23)	0.05 (-0.05 to 0.15)	2 RCTs: significant increases in serum HDL cholesterol within both groups 1 RCT: significant increase within LC group 3 RCTs: non-significant changes within both groups 4 RCTs: did not report within-group statistical analysis

Annex 18: Adverse events

Table A18.1: Adverse events reported in primary studies included in 4 prioritised systematic reviews with meta-analyses

Primary study lead author (year)	Adverse events reported
Brunerova, 2007	No gastro-intestinal or other adverse events reported.
Daly, 2006	No adverse events reported.
Esposito, 2009	Mild: gastroenteritis (9/13; lower carbohydrate (LC)/higher carbohydrate (HC)), nausea (5/3), vomiting (3/2), headache (4/6), fever (3/1), fatigue (5/4). Serious: atrial fibrillation (1/0), pneumonia (0/1). The incidence of adverse events during the treatment phase was similar in both groups: 23 participants (21%) in the LC group and 25 participants (23%) in the HC group reported at least 1 adverse event.
Goday, 2016	No serious adverse events reported. Mild adverse events reported by 80% of the LC group compared with 41% of the participants in the HC group ($p<0.001$). Among the pre-defined adverse events: asthenia, headache, nausea and vomiting were more common in the LC group at 2 weeks (all $p<0.05$). The number of participants reporting these adverse events in the LC group declined at last follow-up. At the end of the study, constipation ($p<0.005$) and orthostatic hypotension ($p<0.05$) were more commonly referred by participants in the LC group (respectively, n=8 and n=6) compared with HC group subjects (both, n=0). Not pre-defined adverse events were more frequent in the LC group at 2 weeks but not at 4 months. Only 1 participant in the LC group discontinued the study because of an adverse event (nausea) associated with ketosis.
Guldbrand, 2012	No serious adverse events reported.
Jenkins, 2014	No serious adverse events reported. Five participants (3/2; LC/HC) reported experiencing hypoglycaemic episodes.
Krebs, 2012	No important adverse events reported.
Pedersen, 2014	No adverse events reported.

Samaha, 2003	One participant in the LC group was hospitalised with chest pain. One participant in the LCD died from complications of hyperosmolar coma, which was thought to be due to poor compliance with drug therapy for diabetes.
Tay, 2014	Two participants in the LC group reported gastrointestinal disorders (constipation and diverticulitis).
Tay, 2015	Three participants (2/1; LC/HC) reported gastrointestinal disorders (constipation and diverticulitis).
Westman, 2008	No significant differences between groups in reported symptomatic adverse events. The most common symptoms experienced at any point during the study were headache (53.1%/46.3%; LC/HC), constipation (53.1%/39.0%), diarrhoea (40.6%/36.6%), insomnia (31.2%/19.5%), and back pain (34.4%/39.0%) ($p>0.05$ for all comparisons).
Wycherley, 2010	No adverse events reported.
Yamada, 2014	Side effects from medication not from diet.

Glossary

Body mass index (BMI)	BMI is used to standardise body weight for different heights. It is calculated by weight in kilograms divided by height in metres squared (weight (kg)/height (m^2)). BMI ranges: • below 18.5 kg/m^2 – underweight range • between 18.5 and 24.9 kg/m^2 – healthy weight range • between 25 and 29.9 kg/m^2 – overweight range • between 30 and 39.9 kg/m^2 – obese range. (For children and young people aged 2 to 18, the BMI calculation takes into account age and sex as well as height and weight.)
Cardiovascular disease (CVD)	A general term for conditions affecting the heart or blood vessels. It can be categorised into 3 types: coronary heart disease, cerebrovascular disease or peripheral vascular disease.
Controlled clinical trial (CCT)	A study design based in a clinical setting that usually has a number of key limitations including lack of randomisation, lack of comparator arm, self-selection and self-reporting by participants.
Commensal	A relationship between two organisms where one benefits from the other without affecting it.
Coronary heart disease (CHD)	A complete or partial narrowing of the coronary arteries which supply the heart muscle. Includes myocardial infarction (MI) and other manifestations of coronary atherosclerosis.
Dietary reference value (DRV)	DRVs describes the distribution of nutrient and energy requirements in a population. They comprise: • Estimated Average Requirement (EAR): half of a group in a population will need more than this amount and half will need less • Reference Nutrient Intake (RNI): the intake that will be adequate to meet the needs of 97.5% of the population • Lower Reference Nutrient Intake (LRNI): the intake which will meet the needs of only 2.5% of the population.

Dyslipidaemia	An abnormal amount of lipids (triacylglycerols, cholesterol or phospholipids) in the blood.
Fasting blood glucose	Level of sugar in the blood after an overnight fast. It can be used to diagnose diabetes or pre-diabetes. NICE defines the following blood glucose levels as: • Normal: Below 5.5 mmol/l (100 mg/dl) • Impaired fasting glucose: Between 5.5 and 6.9 mmol/L (between 100 mg/dl and 125 mg/dl) • Diabetic: 7.0 mmol/L and above (126 mg/dl and above) (Type 2 diabetes: prevention in people at high risk | NICE Public Health Guideline 38; NICE. Published July 12, 2012)
Fasting insulin	Concentration of insulin in the blood after an overnight fast.
Fixed-effects model	A model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect.
Food matrix	The nutrient and non-nutrient components of foods and their molecular relationships to each other.
Glucose tolerance	Ability of the body to absorb and use glucose.
Glycated haemoglobin (HbA1c)	Provides a measure of average plasma glucose concentration.
Hazard ratio (HR)	Comparison of the effect of different variables on survival or other outcomes that develop over time.
Heterogeneity	The variation in study outcomes between studies. Heterogeneity is used generically to refer to any type of significant variability between studies contributing to a meta-analysis that renders the data inappropriate for pooling. This may include heterogeneity in diagnostic procedure, intervention strategy, outcome measures, population, study samples, or study methods. The term heterogeneity can also refer to differences in study findings. Statistical tests can be applied to compare study findings to determine whether differences between the findings are statistically significant. For example, significant heterogeneity between estimates of effect from intervention studies suggests that the studies are not

	estimating a single common effect. In the presence of significant heterogeneity, it is more appropriate to describe the variations in study findings than to attempt to combine the findings into one overall estimate of effect.
High density lipoprotein (HDL) cholesterol	Carries cholesterol away from the cells and back to the liver, where it is either broken down or passed out of the body as a waste product; for this reason, HDL is referred to as "good cholesterol", and higher concentrations are better.
Hyperdyslipidaemia	Increased concentration of lipids in the blood; associated with a number of metabolic diseases.
Insulin resistance	Occurs when cells of the body do not respond properly to the hormone insulin.
Intermediate markers	A marker used in place of a clinical endpoint or disease that is assumed to be representative of that clinical endpoint or disease.
Ketogenic diet	A very low-carbohydrate eating regime that promotes metabolism of fat to ketone bodies rather than carbohydrate to glucose as the body’s main source of energy.
Lignin	A chemical compound present in structural materials, such as the cell walls of many plants, which contributes to their rigidity.
Low density lipoprotein (LDL) cholesterol	Carries cholesterol to the cells that need it. If there is too much cholesterol for the cells to use, it can build up in the artery walls and, over time, narrowing them and reducing blood flow. For this reason, LDL is known as ‘bad cholesterol’.
Meta-analysis (MA)	A quantitative pooling of estimates of effect of an exposure on a given outcome, from different studies identified from a systematic review of the literature. MA is a specific method of statistical synthesis that is used in some systematic reviews, where the results from several studies are quantitatively combined and summarised. The pooled estimate of effect from a MA is more precise (that is, has narrower confidence intervals) than the findings of each of the individual contributing studies, because of the greater statistical power of the pooled sample.

Metabolic syndrome	Medical term for a cluster of conditions that occur together and include high blood pressure, dyslipidaemia and obesity. Metabolic syndrome increases the risk of type 2 diabetes, coronary heart disease and stroke.
Monounsaturated fatty acid (MUFA)	Unsaturated fats have some of the hydrogen atoms missing and have been replaced by a double bond between the carbon atoms. If there is one double bond, the fat is known as a monounsaturated fatty acid.
Network meta-analysis (NMA)	Compares multiple interventions by combining direct evidence from trials comparing 2 interventions with indirect evidence from trials with a common comparator.
Peripheral vascular disease	Results from narrowing or blockage in the arteries to the limbs (usually the legs) and aortic disease, which includes conditions that affect the aorta, including aortic aneurysm and carotid arterial narrowing.
Polyunsaturated fatty acid (PUFA)	Unsaturated fats have some of the hydrogen atoms missing and have been replaced by a double bond between the carbon atoms. If there is more than one double bond the fat is known as a polyunsaturated fatty acid.
Random-effects model	A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.
Randomised controlled trial (RCT)	An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).
Risk factor	Social, economic or biological status, behaviours or environments which are associated with or cause increased susceptibility to a specific disease, ill health, or injury.
Risk of bias	Relates to the quality of a study and is an essential component of a systematic review across studies.

Saturated fat	A fat that has as many hydrogen atoms as it can hold (that is, ‘saturated’ with hydrogen atoms). When hydrogen atoms are missing, carbon atoms form double bonds. Generally saturated fats are solid at room temperature.
Sensitivity analysis	An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.
Subgroup analysis	Analysis that is repeated for a subset of participants (such as male or female) or for a subset of studies (such as differing carbohydrate intakes, low, moderate or high).
Statin	A medicine that can help lower the level of LDL cholesterol in the blood.
Stroke	A serious life-threatening medical condition that occurs when blood supply to part of the brain is cut off.
Systematic review (SR)	Method of identifying, appraising and synthesising research evidence. The aim is to evaluate and interpret all the available research that is relevant to a particular review question. It differs from a traditional literature review in that the latter describes and appraises previous work but does not specify methods by which the reviewed studies were identified, selected, or evaluated. In a SR, the scope (for example, the review question and any sub-questions and/or subgroup analyses) is defined in advance, and the methods to be used at each step are specified. The steps include: a comprehensive search to find all relevant studies; the use of criteria to include or exclude studies; and the application of established standards to appraise study quality. A SR also makes explicit the methods of extracting and synthesising study findings.
Total cholesterol:HDL cholesterol ratio	Provides more information on an individual’s CHD risk by dividing total cholesterol by HDL cholesterol. A ratio above 6 is considered high risk - the lower this figure is the better.
Triacylglycerol	Fats in foods are predominantly in the form of triacylglycerol. They are formed of glycerol and 3 fatty acids. Also called triacylglyceride.

Abbreviations

ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
ALA	alpha-linolenic acid
AMSTAR	A Measurement Tool to Assess systematic Reviews
anti-GAD	antibodies to glutamic acid decarboxylase
anti-IA2	antibodies to islet antigen 2
ASI	angiotensin system inhibition
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BW	body weight
CAB	Commonwealth Agricultural Bureaux
CCT	controlled clinical trial
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	Coronary heart disease
CHO	carbohydrate
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMA	Committee on Medical Aspects of Food and Nutrition Policy
CVD	cardiovascular disease
DARE	Database of Abstracts of Reviews of Effects
DBP	diastolic blood pressure
df	degree of freedom

DP	degree of polymerisation
DPP-4	dipeptidyl peptidase 4
DRV	dietary reference value
EAD	European Association for Diabetes
eGFR	estimated glomerular infiltration rate
EMBASE	Excerpta Medica Database
FAO	Food and Agriculture Organization of the United Nations
FBG	fasting blood glucose
FFQ	food frequency questionnaire
FPG	fasting plasma glucose
GFR	glomerular filtration rate
GI	glycaemic index
GL	glycaemic load
GLP-1	glucagon-like peptide
GRADE	Grading of Recommendations Assessment Development and Evaluations
HbA1c	glycated haemoglobin
HC	higher carbohydrate
HCLF	high-carbohydrate low-fat
HDL	high density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
HPD	high protein diet
IQR	interquartile range
ITT	Intention to treat
kcal	kilocalorie
kJ	kilojoule

LC	lower carbohydrate
LCD	lower carbohydrate diet
LDL	low density lipoprotein cholesterol
LFD	low fat diet
LPD	low protein diet
MA	meta-analysis
MCD	moderate carbohydrate diet
MES	medication effect score
MI	myocardial infarction
MJ	megajoule
MODY	maturity onset diabetes of the young
MUFA	monounsaturated fatty acids
NCVIN	National Cardiovascular Intelligence Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	Noninsulin-dependent diabetes mellitus
NMA	network meta-analysis
NR	not reported
OGTT	oral glucose tolerance test
PA	pooled analysis
PHE	Public Health England
PP	per protocol
PUFA	polyunsaturated fatty acids
QoL	quality of life
RCT	randomised controlled trial
RNI	reference nutrient intake

RoB	risk of bias
RR	relative risk
SACN	Scientific Advisory Committee on Nutrition
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
SFA	saturated fatty acids
SI	International System of Units
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
SSNAP	Sentinel Stroke National Audit Programme
SUCRA	surface under cumulative ranking curves
T1D	type 1 diabetes
T2D	type 2 diabetes
TE	total energy
TRIP	Turning Research into Practice
USDA	US Department of Agriculture
USDHHS	US Department of Health and Human Services
VLCD	very low calorie diet
VLCKD	very low calorie ketogenic diet
vs	versus
WHO	World Health Organization
WKS	weeks
WG	working group
WMD	weighted mean difference