Lower carbohydrate diets for adults with type 2 diabetes

Contents

Membership of joint working group on lower carbohydrate diets for adults with type 2 diabetes

Co-Chairs

Professor Ian Macdonald	Professor of Metabolic Physiology, School of Life Sciences, University of Nottingham (SACN member)
Mr Douglas Twenefour	Deputy Head of Care, Diabetes UK

Members

Professor Peter Aggett	Emeritus Professor and Past Head of Lancashire School of Postgraduate Medicine and Health, University of Central Lancashire; Honorary Professor, School of Medicine, Lancaster University (past SACN member)
Dr Pamela Dyson	Research dietitian, Oxford Centre for Diabetes, Endocrinology and Metabolism (nominated by British Dietetic Association)
Professor Nita Forouhi	Programme Leader and Consultant Public Health Physician, Professor of Population Health and Nutrition, MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine (nominated by Diabetes UK)
Dr Darren Greenwood	Senior Lecturer in Biostatistics, University of Leeds (SACN member)
Dr Rachel Pryke	General practitioner, Redditch (nominated by Royal College of General Practitioners)
Professor Roy Taylor	Professor of Medicine and Metabolism, Newcastle University (nominated by Royal College of Physicians)
Mrs Ruth Waxman	Lay member(nominated by Diabetes UK)
Professor Ian Young	Professor of Medicine, Queen's University Belfast (SACN member)

Secretariat (PHE)

Dr Adrienne Cullum

Ms Estella Hung (*from September 2019*)

Ms Emma Jeffcock *(from May 2019)*

Ms Goda Kijauskaite *(until July 2019)*

Professor Louis Levy

Ms Mamta Singh

Observers

Ms Emily Chan (Food Standards Agency, Northern Ireland)

Ms Kleio Bathrellou (Department of Health and Social Care)

Ms Monica Desai (National Institute for Health and Care Excellence)

Ms Alison Diamond (Scottish Government)

Ms Sarah Rowles (Welsh Government)

Ms Lorraine Shuker (NHSE/I)

Membership of SACN

Chair

Professor Ann Prentice | Honorary Professor of Global Nutrition and Health, MRC Nutrition and Bone Health Research Group, Cambridge (formerly Director of MRC Elsie Widdowson Laboratory, Cambridge)

Members

Ms Gill Fine | Public Health Nutritionist

Dr Darren Greenwood | Senior Lecturer in Biostatistics, University of Leeds

Professor Paul Haggarty | Deputy Director, Rowett Institute of Nutrition and Health, University of Aberdeen

Professor Susan Jebb | Professor of Diet and Population Health, University of Oxford

Professor Mairead Kiely | Head of School of Food and Nutritional Sciences, University College Cork

Professor Susan Lanham-New | Head of the Nutritional Sciences Department, University of Surrey

Professor Julie Lovegrove | Professor of Human Nutrition, Head of the Hugh Sinclair Unit of Human Nutrition and Deputy Director for the Institute for Cardiovascular & Metabolic Research, University of Reading

Professor Ian Macdonald | Professor of Metabolic Physiology, School of Life Sciences, University of Nottingham

Dr David Mela (Industry member) | Industry member, retired

Professor Ken Ong | Professor of Paediatric Epidemiology, MRC Epidemiology Unit and Department of Paediatrics, University of Cambridge

Mrs Gemma Paramor | Lay member

Professor Lucilla Poston | Tommy's Professor of Maternal and Fetal Health, Head of School of Life Course, King's College London

Professor Hilary Powers	Professor Emeritus of Nutritional Biochemistry, Department of Oncology and Metabolism, University of Sheffield
Professor Sian Robinson	Professor of Lifecourse and Lifestyle, Newcastle University
Dr Stella Walsh	Lay member
Professor Charlotte Wright	Professor of Community Child Health, School of Medicine Dentistry and Nursing, University of Glasgow
Professor Ian Young	Professor of Medicine, Queen's University Belfast

Secretariat

Dr Adrienne Cullum

Dr Daphne Duval

Ms Rachel Elsom

Ms Estella Hung

Ms Emma Jeffcock

Ms Emma Peacock

Ms Mamta Singh

Mr Heiko Stolte

Observers

Ms Emily Chan (Food Standards Agency Northern Ireland)

Dr Naresh Chada (Department of Health, Social Services and Public Safety, Northern Ireland)

Professor Louis Levy (Public Health England)

Ms Laura Wilson (Food Standards Agency Scotland)

Ms Sarah Rowles (Department of Health and Social Services, Wales)

1 Introduction

1.1   The purpose of this report is to review the evidence on lower carbohydrate diets compared to current UK government advice for adults with type 2 diabetes (T2D). It was initiated in 2017, in response to a request from Public Health England (PHE), in recognition that such diets are gaining attention and increasingly being promoted.

1.2   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, Royal College of Physicians and 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 also 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.

1.3   This draft report was developed using SACN process and signed off by SACN.

Terms of reference

1.4   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.

1.5   Current UK government advice on carbohydrate intake is based on recommendations made by SACN following its review on carbohydrates and health (SACN, 2015).

1.6   Current UK government advice for the general population is that approximately 50% of total dietary energy should be obtained from carbohydrates, mainly from starchy foods consisting of high fibre or wholegrain food where possible. It is recommended that average population intake of free sugars should not exceed 5% of total dietary energy and that adults should achieve a daily dietary fibre intake of 30g per day. 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.

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

1.8   The markers and clinical outcomes of T2D considered 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 changes in medication and diabetes-related symptoms. Further information on these outcomes and the basis for their selection is explained in chapter 4.

1.9   For the outcome of body weight, only studies with a duration of at least 12 months were considered. For all other outcomes, studies with a minimum duration of 3 months were considered (further details in chapter 4).

1.10 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 on carbohydrates

2.1 The background information on carbohydrates summarised in this chapter is 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 carbohydrate 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 (see Table 2.1): sugars, including mono- and di-saccharides (DP 1-2); oligosaccharides (DP 3-9); and polysaccharides (DP >9).

Table 2.1: Classification of carbohydrates based on their chemistry (FAO/WHO, 1998)

Class (DP)	Subgroup	Components
Sugars (DP 1-2)	Monosaccharides	Glucose, fructose, galactose
	Disaccharides	Sucrose, lactose, maltose
	Polyols	Sorbitol, mannitol
Oligosaccharides (DP 3-9)	Malto-oligosaccharides	Maltodextrins
	Other oligosaccharides	Raffinose, stachyose, fructo-oligosaccharides
Polysaccharides (DP >9)	Starch	Amylose, amylopectin, modified starches
	Non-starch polysaccharides	Cellulose, hemicellulose, pectins, hydrocolloids

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 (SACN, 2015).

2.5 Starch is a polysaccharide of glucose monomers and is the principal carbohydrate in most diets.

2.6   Dietary fibre includes constituents of plant cell walls, such as cellulose, and is the most diverse of the carbohydrate groups (SACN, 2015). The SACN report on 'Carbohydrates and Health' (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.

2.7   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.

2.8   Carbohydrates can also be classified according to their digestion and absorption in the human 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.

2.9   The terms 'simple' and 'complex' carbohydrates are commonly used in the literature when considering dietary carbohydrate content. These terms are not scientifically defined and were not used in the SACN report on 'Carbohydrates and Health' (SACN, 2015) and are not used in this report. The following terms are used to describe carbohydrates:

- Free sugars — these include the monosaccharides glucose, fructose, and galactose, and the disaccharides (which include sucrose and lactose). They refer to those added by food manufacturers, cooks or consumers to food and include those sugars naturally found in honey, syrups and unsweetened fruit juice. The term does not include sugars naturally found in milk and milk products.
- Starches — polymers of glucose, found in foods such as rice, bread, pasta and potatoes.
- Dietary fibres — defined in paragraph 2.6.

Digestion and absorption

2.10 Digestion of starch begins in the mouth, by the action of salivary amylase, but takes place mainly in the small intestine where it is hydrolysed by pancreatic amylase into maltose, maltotriose and α-dextrins. These are further hydrolysed into their component monosaccharides by enzymes expressed on the brush border of the small intestinal cells.

2.11 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 (SACN, 2015).

2.12 Some carbohydrates (non-digestible carbohydrates) contain glycosidic linkages that are not hydrolysed in the small intestine and 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

2.13 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.

2.14 Glucose is under control of the hormone insulin which is produced by beta-cells in the pancreas and is released in response to glucose absorption. The plasma concentration of insulin increases immediately after the ingestion of glucose and in some tissues (for example, adipose tissue, skeletal muscle) the cellular uptake of glucose is insulin-dependent. Fructose uptake into tissues is not insulin-dependent (SACN, 2015).

2.15 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

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

2.17 GI is a relative measure of the capillary blood glucose response to a specific food compared with the response to a reference food with the same amount of available carbohydrate (either pure glucose or an alternative carbohydrate food such as white bread). GI ranks (from 0 to 100) how quickly a carbohydrate-containing food raises blood glucose concentration after consumption (Jenkins et al, 1981). Carbohydrates with a low GI value (55 or less), which include most fruits, vegetables, nuts and legumes, are more slowly digested, absorbed and metabolised and cause a lower and slower rise in blood glucose and, therefore usually, insulin. Carbohydrate foods with a high GI cause a more rapid increase in blood glucose. High GI foods include refined grains, potatoes, and sugar-sweetened beverages.

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

2.19 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).

3 Background on type 2 diabetes

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

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

3.3   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.

3.4   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, 2019a). T1D, gestational diabetes and MODY are not considered further in this report.

3.5   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, 2019a). 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 obesity (Hauner, 2010), a modifiable risk factor.

3.6   Symptoms of diabetes include frequent urination, extreme thirst, tiredness, unplanned weight loss and infection such as genital thrush. These symptoms are less pronounced in people with T2D than T1D and 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.

3.7   Diagnosis of T2D is on the basis of elevated blood glucose concentrations (fasting concentration of 7.0 mmol/L or more or post prandial concentration of 11.1 mmol/L or more) (WHO, 2006) or an elevated HbA1c concentration (often reported as a percentage of red blood cells that are glycated) (48 mmol/mol or more; 6.5% or more) (WHO, 2011). These indices are markers of impaired control of blood glucose and associated metabolic processes (usually referred to as impaired glycaemic control).

3.8   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).

UK and international recommendations for management of T2D

3.9   In England, NICE has issued guidelines for the identification, diagnosis and management of T2D (NICE, 2019a). The Scottish Intercollegiate Guidelines Network (SIGN) have also issued guidelines on management of diabetes (SIGN, 2019).

3.10   The aim of diabetes management and treatment is to reduce and maintain HbA1c concentration at a value below the cut-off for the definition of T2D. Although a reduction below the threshold for the definition of T2D is the ultimate aim, any reduction in HbA1c reflects an improvement in the degree of control of T2D.

3.11   Reduction of blood lipids and blood pressure are also important treatment goals.

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

3.13   Currently, there is no cure for T2D but data from dietary weight management programmes and bariatric surgery confirm that weight loss can result in remission (Diabetes UK, 2018b). The DiRECT study, a UK primary care-led weight management intervention for people with T2D of <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

3.14 A reduction in energy (calorie) intake is an important part of the behavioural interventions recommended to people with T2D who have overweight or obesity. The aim of reducing energy intake is weight loss, which in turn improves glycaemic control. For example, NICE (2019b: [NG28]) recommends that for adults with T2D who have overweight, 'set an initial body weight loss target of 5 to 10%'.

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

3.16 In England, NICE (2019b: [NG28]) recommends a healthy dietary pattern, comparable to national recommendations for the general population, for people with T2D. This reflects the SACN (2015: Section 11.5) recommendation for carbohydrate intake of approximately 50% of total dietary energy. Current government advice for the general population is outlined in Annex 1 (Table A1.1). NICE (2019b: [NG28]) 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'.

3.17 SIGN (2017: [116]) recommends that individuals with T2D 'are given dietary choices for achieving weight loss that may also improve glycaemic control. Options include calorie 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)'.

3.18 International guidelines vary in relation to the amount of carbohydrate recommended for people with T2D (see Table 3.1, below). Diabetes UK, the ADA and Diabetes Australia have made dietary recommendations that focus more on foods and overall dietary patterns.

3.19 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).

3.20   Both Diabetes UK and the ADA emphasise tailoring advice to the individual. Diabetes UK and ADA note the lack of clear evidence for a specific dietary intake of carbohydrate for those with T2D (Diabetes UK (2018a), ADA (2019b)). The ADA recommends that 'reductions in overall carbohydrate intake may be applied in a variety of eating patterns that meet individual needs and preferences' and that 'for select adults 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'.

3.21   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; USDOH & USDA, 2015; Reynolds et al, 2019). Carbohydrates that are associated with poorer health outcomes include sugar, 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; USDOH & USDA, 2015).

3.22   Macronutrient recommendations for adults with T2D, as recommended by NICE, SIGN and a range of diabetes organisations are summarised in Table 3.1 below.

Table 3.1: UK and international macronutrient recommendations for adults with T2D

Organisation	Macronutrient (% total dietary energy)		
	Carbohydrate	**Total fat**	**Protein**
National Institute for Clinical Excellence (NICE)*	50	35	
Scottish Intercollegiate Guidelines Network (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
American Diabetes Association (ADA)	Individualise	20 to 35	15 to 20
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 recommendations.
**Defined as <130g/day or <26% total energy intake derived from carbohydrate.
Data from Diabetes UK (2018a), SIGN (2017), ADA (2019b), Sievenpiper et al (2018), Mann et al (2004), Diabetes Australia (2015), Diabetes Australia (2018), NICE (2019).

4 Markers and clinical outcomes of type 2 diabetes

Selection of primary and secondary outcomes

4.1   The primary outcomes considered in this review are body weight and HbA1c.

4.2   The secondary outcomes considered are fasting plasma glucose, blood lipid profiles and changes in medication and diabetes-related symptoms.

4.3   One of the aims of the 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 blood pressure. Although blood pressure is an important risk factor for CVD, it was not included as an outcome measure since there is clear evidence that a reduction in body weight is the primary driver for a decrease in blood pressure. In contrast with blood lipids, changes in dietary macronutrient composition were not considered likely to have independent effects on blood pressure.

4.4   Although blood pressure was not included as an outcome in this report, blood pressure reduction is an important factor that should be considered in the overall health of adults with T2D.

Study duration

4.5   For the outcome of body weight, only studies with a duration of at least 12 months were considered (see paragraph 4.6). For all other outcomes, studies with a minimum duration of 3 months were considered (see paragraph 4.9).

Primary outcomes

Body weight

4.6   Ninety percent of adults with T2D in the UK have overweight or obesity (Diabetes UK, 2018c). Interventions aim, therefore, to support people to achieve and maintain a healthy body weight. Many short-term interventions are able to achieve weight loss but the maintenance of weight loss is challenging (Miller & Brennan, 2015). Therefore, for the outcome of body weight, only studies with a minimum duration of 12 months were specified in the selection criteria and were considered in grading the evidence and drawing conclusions.

If the eligible evidence also included results of shorter-term studies on change in body weight, then these were reported for completeness but were not considered in grading the evidence for this outcome.

HbA1c

4.7 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.

4.8 In the UK, the cut-off HbA1c concentration for the diagnosis of T2D is 48 mmol/mol (6.5%). HbA1c concentrations for non-diabetic hyperglycaemia are between 42 and 47.9 mmol/mol (6.0 to 6.5%), and concentrations below 42 mmol/mol (6.0%) are regarded as non-diabetic (NICE, 2017).

4.9 Since the life-cycle of red blood cells (containing the haemoglobin) in the circulation is approximately 100 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

Fasting plasma glucose

4.10 Although HbA1c was the primary outcome related to glycaemic control considered in this review, 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 concentration of 7.0 mmol/L is the cut-off for diagnosis of T2D, 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).

Blood lipids

4.11 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 or blood fats such as non-HDL cholesterol and triacylglycerols. 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).

4.12   To assess the effects of lower carbohydrate diets on fasting lipid profiles in people with T2D, the following outcomes 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.

Change in medication use and diabetes-related symptoms

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

5 Methods

Eligibility criteria and literature search

5.1   This report is based on evidence provided by systematic reviews (SRs) with meta-analyses (MAs). 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.

5.2   SACN's Framework for the Evaluation of Evidence (SACN, 2012) was used as the basis for assessing the evidence. The framework is based on an evidence hierarchy which is used to judge the strength of the evidence according to study design. Most weight is placed on evidence from randomised controlled trials (RCTs) since well-conducted RCTs minimise the potential for selection bias and confounding. Less weight is placed on observational studies because such studies 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 evidence than other study designs (case-control, cross-sectional and case reports).

Inclusion criteria

5.3   The Knowledge and Library Services team (PHE) conducted an online database search for SRs, MAs and pooled analyses of RCTs and prospective cohort studies comparing the impact of lower versus higher carbohydrate diets on markers and clinical outcomes of T2D. Details of the search terms are provided in Annex 2 (Table A2.1).

5.4   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).

5.5   Only SRs that included studies that recruited people with pre-diagnosed T2D (as defined in the primary RCTs) when they entered the study were considered.

5.6   For the primary outcome of body weight, only studies with a minimum duration of 12 months (which reflects longer-term maintenance of weight loss) were considered (see paragraph 4.6, chapter 4). For all other outcomes, studies with a minimum duration of 3 months were considered.

Exclusion criteria

5.7   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/book chapters, opinion pieces, information from websites, reports and other non-peer reviewed articles.

5.8   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 excluded.

Evidence from clinical practice studies

5.9   A number of clinical studies (including Saslow et al (2017); Bhanpuri et al (2018); Hallberg et al (2018), Athinarayanan et al (2019)) and case reviews (Unwin & Tobin, 2015) have assessed the effectiveness of lower carbohydrate diets on glycaemic control and other markers in adults with T2D. These are largely based in primary or secondary care clinic settings or use data from participants self-enrolled in commercial dietary programmes. The study design employed in such published research includes quasi-experimental studies, non-randomised trials, single-arm trials or experiences in clinical practice. Some of the key limitations of these studies are: lack of randomisation, lack of a comparator arm and self-selection (for example, participants may choose a particular study or study arm).

5.10   These studies were not considered in this report because of the number of limitations associated with this study type. They also did not meet the inclusion criteria for study selection (see paragraphs 5.3 to 5.5).

Literature search

5.11   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.

5.12   Interested parties were also invited to highlight any additional evidence (including key RCTs published after the most recent SRs/MAs) to that identified by the PHE literature search (and which satisfied the inclusion criteria) in a call for evidence published on the SACN website (from 9 February to 7 March 2018).

5.13   Reference lists of all included publications (identified through the online database search or highlighted by interested parties, up to September 2018) were hand-searched.

5.14   Reference lists of relevant reviews by other international organisations were also considered.

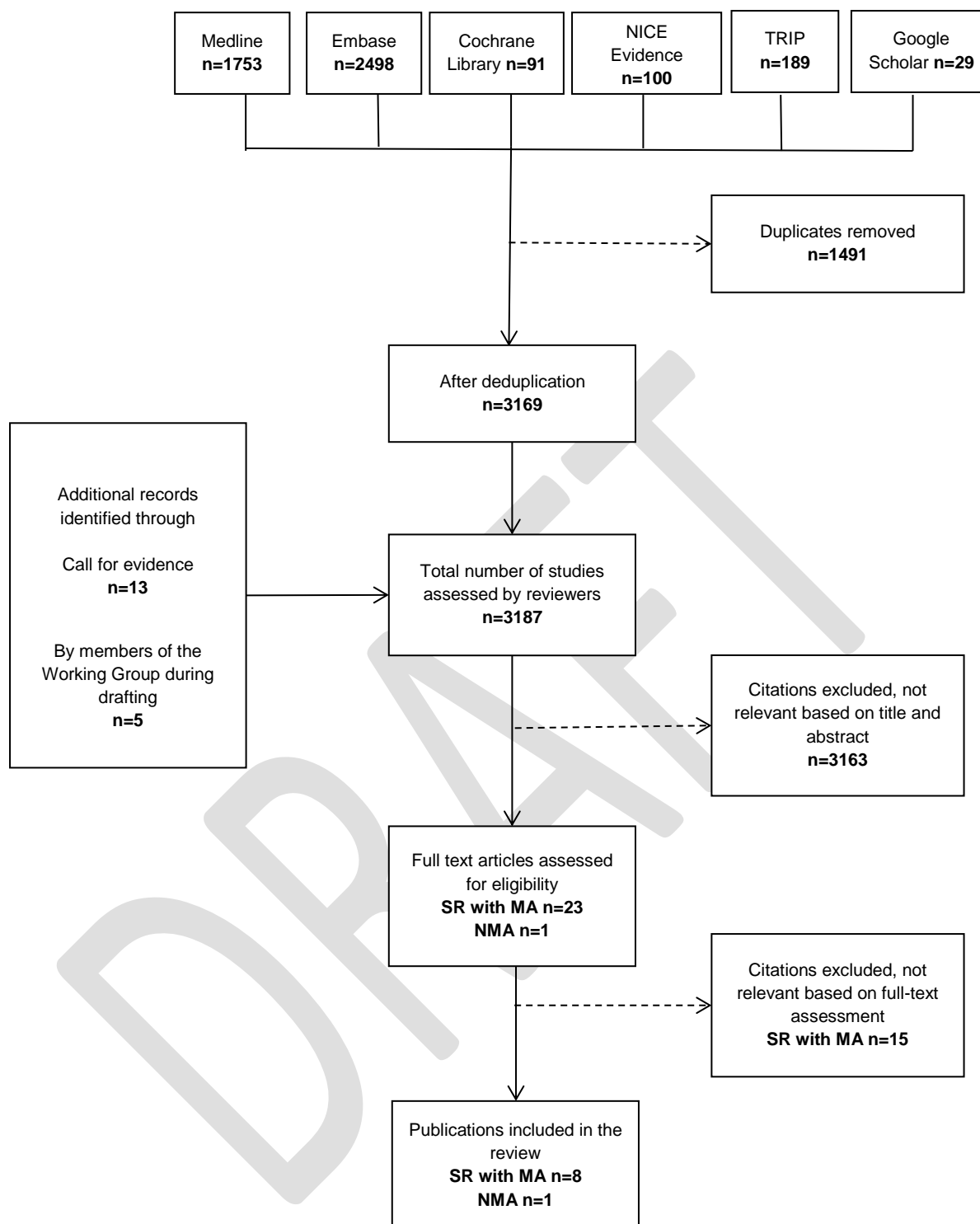## Consideration of evidence published after the literature search

5.15   The draft report has been made available for public consultation and interested parties are invited to alert SACN to any evidence that it may have missed.

5.16   Any evidence highlighted through the consultation process or published after September 2018 will be considered by the committee.

5.17   The report will be amended if newly available evidence adds to existing work or changes existing conclusions.

Selection of studies

5.18   Literature search: After removing duplicates, titles and abstracts of the identified publications were screened independently by 2 reviewers for eligibility. Differences were resolved by discussion. Publications were rejected on initial screen if the reviewers could determine from the title and abstract that they did not meet the inclusion criteria. Full-texts of potentially eligible publications were obtained and again screened by 2 reviewers with differences resolved by discussion. Where uncertainty remained, advice was sought from the WG.

5.19   The online database search identified 3169 abstracts which were screened for eligibility. Of these, full texts of 19 potentially relevant SRs with MAs were retrieved and screened and 11 met the inclusion criteria. Details of the studies excluded on the 1st screening and reasons for exclusion are provided in Annex 3 (Table A3.1). Two subsequent publications that met the inclusion criteria were identified by WG members: 1 SR with MA and 1 network meta-analysis (NMA). NMAs compare multiple interventions by combining direct evidence from trials comparing 2 interventions with indirect evidence from trials with a common comparator.

5.20   The 12 identified SRs with MAs and the NMA were of RCTs (no SRs of prospective cohort studies were identified).

5.21   Call for evidence: Three responses citing 13 publications were received in response 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.

5.22   Post call for evidence: Seven of the SRs with MAs identified by the PHE literature search (see paragraph 5.20) were excluded (Garg, 1998; Anderson et al, 2004; Nield et al, 2007; Kirk et al, 2008; Kodama et al, 2009; Castaneda-Gonzalez et al, 2011; Ajala et al, 2013) either because the majority of the included RCTs were of less than 3 months duration or because they did not

offer any additional information to that covered by the more recent SRs with MAs.

5.23   Three additional SRs with MAs (Korsmo-Haugen et al, 2018; Sainsbury et al, 2018; van Zuuren et al, 2018) were subsequently identified by members of the WG.

5.24   The 2 RCTs identified in the call for evidence were not considered separately because 1 (Tay et al, 2018) was included in the SR by van Zuuren et al (2018) and the other (Saslow et al, 2017) was included in a SR (McArdle et al, 2018) published after September 2018 (to be considered post-consultation).

5.25   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 further consideration.

5.26   Figure 5.1 displays the flow diagram for inclusion of studies.

| Medline n=1753 | Embase n=2498 | Cochrane Library n=91 | NICE Evidence n=100 | TRIP n=189 | Google Scholar n=29 |

Duplicates removed
n=1491

After deduplication
n=3169

Additional records identified through

Call for evidence
n=13

By members of the Working Group during drafting
n=5

Total number of studies assessed by reviewers
n=3187

Citations excluded, not relevant based on title and abstract
n=3163

Full text articles assessed for eligibility
SR with MA n=23
NMA n=1

Citations excluded, not relevant based on full-text assessment
SR with MA n=15

Publications included in the review
SR with MA n=8
NMA n=1

Figure 5.1: Flow diagram showing the number of publications assessed for eligibility and included in the review.

Data extraction

5.27   The following data from all 8 SRs with MAs and the 1 NMA were extracted and summarised (see Annex 4, Tables A4.1 to A4.2): first author, year of publication, research question, study design, location, funding, declarations of interest, inclusion/exclusion criteria, statistical analysis, assessment of study quality, total number of primary RCTs, total number of participants, study duration, demographics and results.

Primary data in the SRs with MAs

5.28   In total, there were 48 publications (relating to 44 primary RCTs) included in the 8 eligible SRs with MAs. Information was extracted from all 48 publications included in the SRs with MAs to enable a more detailed assessment (see Annex 5, Tables A5.1 to A5.3).

5.29   Information was not extracted from the primary studies 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 include a comparison of lower versus higher carbohydrate diets.

5.30   Data extracted from all publications in the 8 SRs with MAs included: sample size; age; inclusion/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 achieved intakes of carbohydrates; dietary fat including saturated fats, polyunsaturated fats (PUFA) and monounsaturated fats (MUFA) and protein (expressed as percentage of total energy and grams per day); prescribed and achieved intakes of energy (kcal per day); duration of T2D and T2D inclusion criteria, medication use; and recommendations for physical activity.

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

5.32   The overlap of publications included in the 8 SRs with MAs, grouped by outcome and then MA, were tabulated (Annex 6, Tables A6.1 to A6.7).

5.33   The extracted data (see paragraph 5.30) were used to prepare bar graphs showing the following comparisons between the lower and higher carbohydrate groups for the primary outcomes (body weight and HbA1c) (see Annex 7, Figures A7.1 to A7.20):

- prescribed and achieved carbohydrate intakes
- difference between intakes of carbohydrate (prescribed versus achieved)

- adherence to prescribed intake of carbohydrate

- macronutrient (carbohydrate, fat, protein) intakes

- energy intakes

- fatty acid intakes (SFAs, PUFAs, MUFAs)

Units of measurement

5.34 Energy intakes were expressed in kilocalories (kcal) with the corresponding SI (International system of units) values in megajoules (MJ) or kilojoules (kJ) in brackets. When expressed in megajoules (MJ) or kilojoules (kJ), they were converted to kilocalories (kcal) for consistency (1 MJ = 239.06 kcal, 1 kJ = 0.239006 kcal).

5.35 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).

5.36 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

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

Definitions of study durations

5.38 Primary RCTs with a duration of ≥3 to <12 months were defined as *shorter term* and those with a duration of ≥12 months were defined as *longer term*.

Definitions of diets containing different amounts of carbohydrate

5.39 There is no universally agreed definition of a 'low carbohydrate diet' and definitions vary across studies. Comparisons in this report were therefore between lower and higher carbohydrate intakes.

5.40 Feinman et al (2015) proposed definitions for diets containing different amounts of carbohydrate intakes regarded as very low, low, moderate or high (adapted from Accurso et al (2008). These categories were defined in both grams per day and as a percentage of TE intake of approximately 2,000 kcal/day (see Table 5.1).

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

Table 5.1: Categories of dietary carbohydrate intakes*

| Description | Amount of carbohydrate | |
	g/day	% TE (based on 2000 kcal/day)
Very low carbohydrate∞	20 to 50	≤10
Low carbohydrate	>50 to <130	>10 to <26
Moderate carbohydrate	130 to 230	26 to 45
High carbohydrate	>230	>45

*Based on Feinman et al (2015) and Accurso et al (2008)
∞Also referred to as ketogenic diets.

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

5.43 Categorisation of a low carbohydrate diet varies between the primary RCTs with some defining it in g/day and some as % TE. In weight loss interventions carbohydrate intake 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 below) which may be low in achieved g/day of carbohydrate but also low in other nutrients and, therefore, relatively high in carbohydrates as % TE.

5.44 Low and very low carbohydrate diets should not be confused with low and very low energy 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 up of formulated products to ensure adequate protein and micronutrient intake.

Grouping of the evidence by outcomes

5.45 Evidence from the eligible 8 SRs with MAs was considered for each of the primary and secondary outcomes and subdivided according to study duration (shorter-term, ≥3 months to <12 months; longer-term, ≥12 months).

Assessment of the evidence

5.46   The 8 SRs with MAs that met the inclusion criteria were considered by the WG. Chapters on the impact of lower carbohydrate diets compared with higher carbohydrate diets on markers and clinical outcomes of T2D were drafted by the secretariat of the WG and provided the basis for the WG's considerations. The final text and conclusions were considered and agreed by SACN. This draft report has been made available for public consultation and the comments received from interested parties will be taken into consideration before the report is finalised.

Evaluation of the quality of the evidence

5.47   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

5.48   The following criteria were considered:

Systematic review and meta-analyses

- scope and aims
- search dates (publication dates of studies included in the reviews or meta-analyses)
- 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 considered within systematic reviews/meta-analyses

- exposure/intervention duration and follow-up
- type of carbohydrates (for example, starch, free sugars, fibre) and types of nutrients replacing carbohydrates (for example, protein, fat) in the lower carbohydrate groups
- prescribed and achieved 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 their 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/association (which may be consistent across studies)
- direction and size of effect and statistical significance
- results of subgroup and sensitivity analyses.

5.49   In accordance with the SACN Framework for the Evaluation of Evidence (SACN, 2012), 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 (SACN, 2019).

AMSTAR 2

5.50   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 discussion.

5.51   AMSTAR 2 includes the following 16 items for evaluation (AMSTAR, 2017):
   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?

5.52   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), about the population (such as medication use, duration since diabetes diagnosis, physical activity), and the intervention (such as prescribed and achieved intakes of carbohydrate, dietary advice, approach, adherence) would be an important consideration in the assessment and interpretation of the evidence.

5.53   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).

5.54   A summary of the AMSTAR 2 assessment is provided in Annex 8 (Table A8.1).

Approach to considering statistical models

5.55   The results of 2 statistical models of MA, fixed effects and random effects, are increasingly being reported in SRs. 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).

5.56   More detailed information on differences between the 2 models can be found in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook).

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

- Where the results of only 1 model (that is, fixed effects or random effects) were stated in a publication, the results of this MA were reported and used to draw conclusions.

- Where the results of both models were stated in a publication, both were reported. The following factors were considered: appropriateness of the model assumptions, the direction and magnitude of the effect, statistical significance and the level of agreement between the models. Where the results of the 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 *Grading of the evidence* below).

Grading of the evidence

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

5.59 Expert judgement, based on the criteria specified in Table 5.3 below, was used to grade the strength of the evidence (*adequate*, *moderate*, *limited*, *inconsistent* or *insufficient*) for the primary and secondary outcomes.

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

5.61 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.

5.62 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 5.3. 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.

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

Table 5.3 Criteria for grading evidence (SACN, 2019)

Strength of evidence	Explanatory notes
Adequate	There is *adequate* evidence to make a decision about the effect/association of a factor(s)/intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, 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 convincing evidence of a consistent significant effect/association in the primary studies considered. Effects/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/follow-ups of randomised controlled trials and/or 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 randomised controlled trials 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 when a meta-analysis or pooled analysis is not conducted, evidence may be considered *adequate* if a total of ≥ 4 randomised controlled trials 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/association of a factor(s)/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 moderate evidence of a consistent significant effect/association in the primary studies considered.

Strength of evidence	Explanatory notes
	Effects/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 randomised controlled trials and/or prospective cohort studies, of moderate quality with sufficient durations/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 randomised controlled trials or 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 when a meta-analysis or pooled analysis was not conducted, evidence may be considered moderate if a total of ≥ 3 randomised controlled trials 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/association of a factor(s)/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/association in the primary studies considered.
	Effects/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 randomised controlled trials and/or prospective cohort studies, of low quality with inadequate

Strength of evidence	Explanatory notes
	durations/follow-ups, included in the identified systematic reviews, meta-analyses and pooled. 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 randomised controlled trials 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.
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 a conclusion.
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 randomised controlled trials or cohort studies were identified. Therefore, it is not possible to draw conclusions.

6 Assessment of the evidence

6.1   Eight 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 consideration.

6.2   After further assessment, only results from 4 SRs with MAs (Huntriss et al, 2018; Korsmo-Haugen et al, 2018; Sainsbury et al, 2018; van Zuuren et al, 2018) were prioritised and used to grade the evidence and draw conclusions. This is because they were more recent, larger (in terms of number of participants) and considered to be of better quality (based on SACN and AMSTAR 2 criteria, see chapter 5) than the older SRs with MAs (Naude et al, 2014; Fan et al, 2016; Meng et al, 2017; Snorgaard et al, 2017). Only 1 primary RCT (Iqbal et al, 2010) that was included in 3 of the older SRs was not covered by the 4 prioritised SRs with MAs.

6.3   The overlap of primary RCTs grouped by outcome and MA is summarised in Annex 6 (Tables A6.1 to A6.7).

6.4   The NMA (Schwingshackl et al, 2018) was also not considered further in grading the evidence 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.

6.5   A summary 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 9.

Overview of the prioritised SRs with MAs

6.6   The various markers and clinical outcomes of T2D considered in each SR with MA are summarised in Annex 10 (Table A10.1). None of the 4 prioritised SRs with MAs considered total cholesterol:HDL cholesterol ratio or reduction in diabetes-related symptoms as outcomes. Only 1 SR with MA (Huntriss et al, 2018) considered change in medication use as an outcome, specifically diabetes medication.

6.7   The main inclusion criteria for each of the 4 prioritised SRs with MAs are provided in Table 6.1 below.

Table 6.1: Main inclusion criteria for the 4 prioritised SRs with MAs

Author (year)	Huntriss et al (2018)	Korsmo-Haugen et al (2018)	Sainsbury et al (2018)	van Zuuren et al (2018)
Search period	Up to June 2016	1983 to January 2016	01 Jan 1980 to 31 August 2016	Up to 21 March 2017
Carbohydrate comparison	Low carbohydrate diet as stated by author; must have achieved lower carbohydrate intake than control group	Diet <40% TE versus diet >40% TE from carbohydrates	Diet ≤45% TE versus diet >45% TE from carbohydrates	Diet ≤40% TE from carbohydrates versus low fat diet (≤30% TE)
Type of study and duration	RCTs (duration not specified) in adults aged ≥18 years with T2D	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	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	RCTs and clinically controlled trials over ≥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)

6.8 In the overview below of the 4 SRs with MAs (paragraphs 6.10 to 6.25), the numeric ranges used by the authors to define lower and higher carbohydrate diets (where stated) are included in brackets. This is followed by classification of these intakes according to carbohydrate categories in square brackets (*very low, low, moderate, high*) (see chapter 5, paragraphs 5.40 to 5.41 and Table 5.1).

6.9 The overall risk of bias analyses of the primary RCTs included in the 4 prioritised SRs with MAs (as assessed by the authors) are also summarised in the overviews below. 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 11 (Tables A11.1 and A11.2).

Huntriss et al (2018)

6.10   Huntriss et al (2018) (18 RCTs, 2204 participants) compared the effects of a lower (not defined) compared to a higher (not defined) carbohydrate diet in the management of T2D. RCTs were included if the lower carbohydrate diet group achieved a lower carbohydrate intake than the higher carbohydrate group (usual care, which included a variety of diets).

6.11   The primary outcome was HbA1c; secondary outcomes were weight, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol, serum HDL cholesterol and changes in diabetes medication.

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

6.13   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)

6.14   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% of total energy [*moderate*]).

6.15   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.

6.16   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.

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

Sainsbury et al (2018)

6.18   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*]) in reducing HbA1c and whether greater restriction of carbohydrate was associated with greater reductions in HbA1c. Although 25 RCTs were included in the study description table, 2 additional studies (Brinkworth et al, 2004; Stern et al, 2004) missing from this table, were included in some MAs.

6.19   The primary outcome was HbA1c; secondary outcomes were weight, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol.

6.20 Meta-analyses were performed for weight change and HbA1c change at 3, 6, 12 and 24 months. All other outcomes were qualitatively evaluated. A subgroup analysis, based on prescribed quantity of carbohydrates (*low, moderate*) was performed at each time point. 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).

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

van Zuuren et al (2018)

6.22 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*]) with low fat diets (defined as ≤30% TE).

6.23 Primary outcomes were HbA1c, fasting plasma glucose, serum total cholesterol, serum triacylglycerol, serum LDL cholesterol and serum HDL cholesterol; body weight was a secondary outcome.

6.24 MAs were performed for change in each outcome at up to 8 weeks, ≥8 to <16 weeks, ≥16 to 26 weeks (approximately 4 to 6 months) and ≥26 weeks (all RCTs in this category were ≥12 months). Sensitivity analyses were performed for all outcomes using a fixed-effects model. Separate sensitivity analyses were also performed that excluded studies at high risk of bias and studies that caused substantial heterogeneity.

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

Overview of primary RCTs included in the prioritised SRs with MAs

6.26 Thirty-six publications were included in the MAs of the 4 SRs. Seven of these related to 3 RCTs reporting at different follow-up time points and/or different outcomes:

1) Parker et al (2002) (3 months); Brinkworth et al (2004) (16 months)
2) Jonasson et al (2014) (outcome: inflammatory markers; 6 months); Guldbrand et al (2012) (24 months)
3) Tay et al (2014) (6 months); Tay et al (2015) (12 months); Tay et al (2018) (24 months)

6.27 In total, 32 primary RCTs were included in the MAs of the 4 SRs.

Characteristics of primary RCTs

6.28   Population characteristics (including age, ethnicity, sex, sample size, BMI, duration since diabetes diagnosis) and details of dietary interventions and physical activity guidance from the 32 RCTs in the 4 SRs are summarised below.

Populations

6.29   Participants in 31 out of 32 primary RCTs were adults (aged ≥18 years) with T2D. One RCT also included participants without T2D. Ten out of 32 RCTs reported ethnicity and, of those, the average number of white participants was 48.3% (range, 14 to 75%). One RCT reported participants as 'predominantly white'. Ethnicity was not reported in 21 RCTs.

6.30   Thirty out of 32 RCTs included both men and women; 2 RCTs included only women. Total sample size ranged from 24 to 419 study participants (mean, n=99).

6.31   Twenty-nine of the 32 RCTs reported BMI of study participants. Of those, 27 RCTs reported similar BMI for both groups. The average BMI was 34 kg/m^2 (range, 25 to 43 kg/m^2) in the lower carbohydrate groups and 35 kg/m^2 (range, 27 to 43 kg/m^2) in the higher carbohydrate groups. One RCT did not report BMI but inclusion criteria specified BMI of 27 to 40 kg/m^2. Two RCTs did not report BMI and it was not clear whether participants with healthy weight were included. One RCT also included participants with healthy weight.

Loss to follow-up

6.32   Thirty out of 32 RCTs reported number of participants lost to follow-up.

6.33   All shorter-term studies (≥3 to <12 months) (16 RCTs) reported loss to follow-up. Of those, 4 reported no loss to follow-up in either dietary groups. The average loss to follow-up was 19% (range, 0 to 34%) in the lower carbohydrate group and 15% (range, 0 to 42%) in the higher carbohydrate group. One RCT did not report separately for each group (8% of participants lost to follow-up).

6.34   Out of the longer-term studies (≥12 months) (16 RCTs), 14 reported loss to follow-up. Of those, 1 reported no loss to follow-up in either dietary group. The average loss to follow-up was 23% (range, 0 to 46%) in the lower carbohydrate group and 22% (range, 0 to 51%) in the higher carbohydrate group.

Medication use

6.35   Details of medication use reported in the primary RCTs is provided in Annex 12 (Table A12.1). Out of 32 RCTs, 27 reported medication use at baseline in

varying levels of detail. Medications included insulin; oral hypoglycaemic agents; lipid-lowering drugs; anticoagulants; and blood pressure lowering drugs.

6.36   Ten RCTs specified diabetes medication as part of the inclusion or exclusion criteria. Out of these: 6 excluded T2D individuals on insulin; 1 stipulated no use of anti-hyperglycaemic medications but did not specify if this included insulin; 3 included only newly-diagnosed T2D individuals who were not being treated with any diabetes medication.

6.37   Out of the 27 RCTs that reported medication use at baseline, 2 did not report on any changes made to medication during the study. Out of 25 RCTs that reported changes: 14 provided statistical analyses (9 between-groups; 1 within group; 4 within and between groups); 11 provided descriptive analyses.

Duration since diabetes diagnosis

6.38   There is a greater possibility of remission (or an effect of a dietary intervention) with shorter versus longer duration since diabetes diagnosis (Steven et al, 2016). Duration since diabetes diagnosis was reported in 15 out of the 32 RCTs. Average duration 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. Two RCTs reported that study participants were 'newly' diagnosed with T2D. Fifteen RCTs did not report duration since diabetes diagnosis.

Physical activity

6.39   Nineteen out of the 32 RCTs included recommendations for physical activity during the study intervention period (see Annex 5, Table A5.3). All participants received the same advice and reported time spent in physical activity did not differ between groups. Advice varied from maintaining usual level of activity (6 RCTs), broad advice consistent with public health guidelines (6 RCTs) or more specific recommendations that included daily or weekly targets (7 RCTs). Thirteen RCTs did not provide any advice on physical activity.

Dietary interventions and approach

6.40   Details of the intervention approach (for example, number of sessions, motivational advice, group or individual discussions) were reported in 27 out of the 32 RCTs. Out of these, 17 RCTs provided one-to-one sessions, 7 provided group sessions and 3 provided a mixture of one-to-one and group sessions. All 27 RCTs reported that the intervention approach was the same in the lower and higher carbohydrate groups. Five RCTs did not report details of the intervention approach.

6.41   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 which contributed to 16 to 60% TE. One RCT reported exclusive use of polyphenol-enriched extra virgin olive oil in the lower carbohydrate group only. One RCT supplemented participants with potassium, sodium, magnesium, calcium and omega-3 fatty acids during 'ketogenic phases' of the intervention and 1 RCT supplemented participants with vanadyl sulphate, chromium dicotinate glycinate and alpha-lipoic acid.

6.42   Few studies reported carbohydrate quality as part of dietary advice: 1 RCT promoted wholegrain carbohydrates; 1 RCT encouraged participants to eliminate simple sugars and prescribed 'complex carbohydrates'; and 1 RCT recommended participants avoid all 'processed carbohydrates – such as bread and pasta'. Two RCTs prescribed 30 g/day and 20 g/day of fibre, respectively, in both diet groups and 1 RCT emphasised fruits and vegetables with high fibre content. Nine RCTs promoted low-GI foods.

Assessment of dietary intakes

6.43   Dietary intakes were self-reported in 28 RCTs using a variety of dietary assessment methods (food diaries, 24-hour recall, food frequency questionnaires). The most common method was the use of food diaries (19 RCTs) although studies differed in number of collection days (3 to 7 days), the most common being 3-days (7 RCTs). Five RCTs reported dietary assessment by use of 24-hour recall method, 2 RCTs used food frequency questionnaires and 2 RCTs used a mixture of methods. Four out of 32 RCTs did not report on how dietary information was collected.

Macronutrient and energy intakes

6.44   Estimated intakes of carbohydrates, fats (total, SFA, PUFA, MUFA), protein and energy, reported in the 32 RCTs included in the MAs of the 4 prioritised SRs, are summarised in Table 6.2. The intake data (range of mean intakes and median) are presented by study duration (except for prescribed carbohydrate intakes): shorter-term (≥3 to <12 months) and longer-term (≥12 months).

Carbohydrate intakes

Prescribed carbohydrate intakes

6.45   Twenty-one RCTs reported prescribed mean carbohydrate intakes in the lower and higher carbohydrate groups. Across studies, these 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 5.1), prescribed intakes ranged from *low* to *high* in both lower and higher carbohydrate groups.

Achieved carbohydrate intakes

6.46   Twenty-seven of the 32 RCTs reported achieved mean carbohydrate intakes either as % TE, absolute amounts (g/day) or both (21 RCTs). Estimated achieved carbohydrate intakes (as % TE and g/day) are presented in Table 6.2. Where RCTs reported achieved carbohydrate intakes as % TE, they were converted to the corresponding value in g/day (or *vice versa* if data on total energy intake was provided).

6.47   According to categories of carbohydrate intakes, only 3 out of 27 RCTs compared *low* versus *high* for achieved mean carbohydrate intakes. The highest number of comparisons (14 RCTs) were between *moderate* and *high* achieved mean carbohydrate intakes (see Figure 6.1). There was also considerable overlap in achieved mean carbohydrate intakes between the lower and higher carbohydrate groups across studies.

6.48   In shorter-term (≥3 to <12 months) studies, estimates of achieved 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, achieved mean intakes expressed as % TE ranged from *low* to *high* in *the* lower carbohydrate groups and *moderate* to *high* in the higher carbohydrate groups; however, when expressed as g/day, carbohydrate categories in the lower carbohydrate groups ranged from *very low* to *moderate.*

6.49   In longer-term (≥12 months) studies, estimates of achieved mean carbohydrate intakes ranged from 18 to 46% TE or 76 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, achieved mean intakes expressed as % TE ranged from *low* to *high* in the lower carbohydrate groups and *moderate* to *high* in the higher carbohydrate groups; however, when expressed as g/day, carbohydrate categories in the lower carbohydrate groups ranged from *low* to *moderate.*

Carbohydrate intakes in primary RCTs included in MAs of 4 prioritised SRs

6.50   The range and categories of carbohydrate intakes (prescribed and achieved) in the primary RCTs included in each of the prioritised 4 SRs is shown in Table 6.3.

6.51   In all 4 SRs with MAs, most comparisons between lower and higher carbohydrate groups by categories of achieved carbohydrate intake were between *moderate* versus *high* (see Table 6.3 and Figure 6.1).

Achieved fat intakes

6.52   Estimated mean intakes (% TE) of total fats, SFAs, PUFAs and MUFAs were higher in the lower compared to the higher carbohydrate groups in shorter-term and longer-term studies.

6.53   In shorter-term (≥3 to <12 months) studies, estimated mean total fat intakes ranged from 18 to 59% TE in the lower carbohydrate groups and 23 to 36% TE in the higher carbohydrate groups.

- Estimated mean SFA intakes ranged from 6 to 20% TE in the lower carbohydrate groups and 8 to 12% TE in the higher carbohydrate groups.

- Estimated mean PUFA intakes ranged from 4 to 9% TE in the lower carbohydrate groups and 5 to 7% TE in the higher carbohydrate groups.

- Estimated mean MUFA intakes ranged from 8 to 17% TE in the lower carbohydrate groups and 10 to 12% TE in the higher carbohydrate groups.

6.54   In longer-term (≥12 months) studies, estimated mean total fat intakes ranged from 31 to 58% TE in the lower carbohydrate groups and 27 to 40% TE in the higher carbohydrate groups.

- Estimated mean SFA intakes ranged from 10 to 19% TE in the lower carbohydrate groups and 8 to 13% TE in the higher carbohydrate groups.

- Estimated mean PUFA intakes ranged from 6 to 13% TE in the lower carbohydrate groups and 4 to 7% TE in the higher carbohydrate groups.

- Estimated mean MUFA intakes ranged from 13 to 25% TE in the lower carbohydrate groups and 11 to 13% TE in the higher carbohydrate groups.

Achieved protein intakes

6.55   Estimated mean protein intakes were higher in the lower compared to the higher carbohydrate groups in the shorter and longer term.

6.56   In shorter-term (≥3 to <12 months) studies, estimated mean protein intakes ranged from 19 to 37% TE in the lower carbohydrate groups and 16 to 23% TE in the higher carbohydrate groups.

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

Achieved energy intakes

6.58   Out of 32 RCTs, 23 prescribed energy (calorie) restriction in 1 or more groups. Prescribed energy restriction in the lower and higher carbohydrate groups was the same in 13 RCTs and differed in 10 RCTs (of those, 6 RCTs prescribed a 500 kcal (2092 kJ) deficit only for the higher carbohydrate group).

6.59   Estimated 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 6.2).

6.60   In shorter-term (≥3 to <12 months) studies, estimated mean energy intakes ranged from 1,273 to 2,029 kcal/day (5,326 to 8,489 kJ/day) (median, 1,557 kcal/day; 6,514 kJ/day) in the lower carbohydrate groups and 1,197 to 1,785 kcal/day (5,008 to 7,468 kJ/day) (median, 1,522 kcal/day; 6,368 kJ/day) in the higher carbohydrate groups.

6.61   In longer-term (≥12 months) studies, estimated mean energy intakes ranged from 1,251 to 2,222 kcal/day (5,234 to 9,297 kJ/day) (median, 1,708 kcal/day; 7,146 kJ/day) in the lower carbohydrate groups and 1,420 to 2,222 kcal/day (5,941 to 9,297 kJ/day) (median, 1757 kcal/day; 7351 kJ/day) in the higher carbohydrate groups.

Table 6.2: Macronutrient and energy intakes in the primary RCTs included in MAs of 4 prioritised SRs

	Duration (number RCTs)	Mean intakes Median (range)[1]	
		Lower carbohydrate groups	Higher carbohydrate groups
Prescribed carbohydrate (% TE)[2] [carbohydrate category]	All (21)	40 (14 to 50) [low to high]	55 (23 to 65) [low to high]
Achieved carbohydrate (% TE) [carbohydrate category]	Shorter-term[3] (13)	38 (13 to 47) [low to high]	50 (41 to 55) [moderate to high]
	Longer-term[4] (14)	39 (18 to 46) [low to high]	48 (43 to 54) [moderate to high]
Achieved carbohydrate (g/day) [carbohydrate category]	Shorter-term[5] (12)	127 (49 to 218) [very low to moderate]	198 (139 to 245) [moderate to high]
	Longer-term[6] (13)	167 (76 to 233) [low to moderate]	210 (156 to 250) [moderate to high]
Achieved Fats (%TE)	Shorter-term		
Total	(13)	40 (18 to 59)	31 (23 to 36)
SFA	(7)	9 (6 to 20)	8 (8 to 12)
PUFA	(5)	5 (4 to 9)	5 (5 to 7)
MUFA	(5)	15 (8 to 17)	11 (10 to 12)
	Longer-term		
Total	(12)	42 (31 to 58)	32 (27 to 40)
SFA	(11)	12 (10 to 19)	10 (8 to 13)
PUFA	(7)	8 (6 to 13)	6 (4 to 7)
MUFA	(8)	16 (13 to 25)	11 (11 to 13)
Achieved protein (% TE)	Shorter-term (13)	26 (19 to 37)	19 (16 to 23)
	Longer-term (11)	23 (16 to 27)	19 (16 to 21)
Achieved energy (kcal/day; kJ/day)	Shorter-term (12)	1557 (1273 to 2029); 6514 (5326 to 8489)	1522 (1197 to 1785); 6368 (5008 to 7468)
	Longer-term (13)	1708 (1251 to 2222); 7146 (5234 to 9297)	1757 (1420 to 2222); 7351 (5941 to 9297)

[1] Median and range of mean intakes.
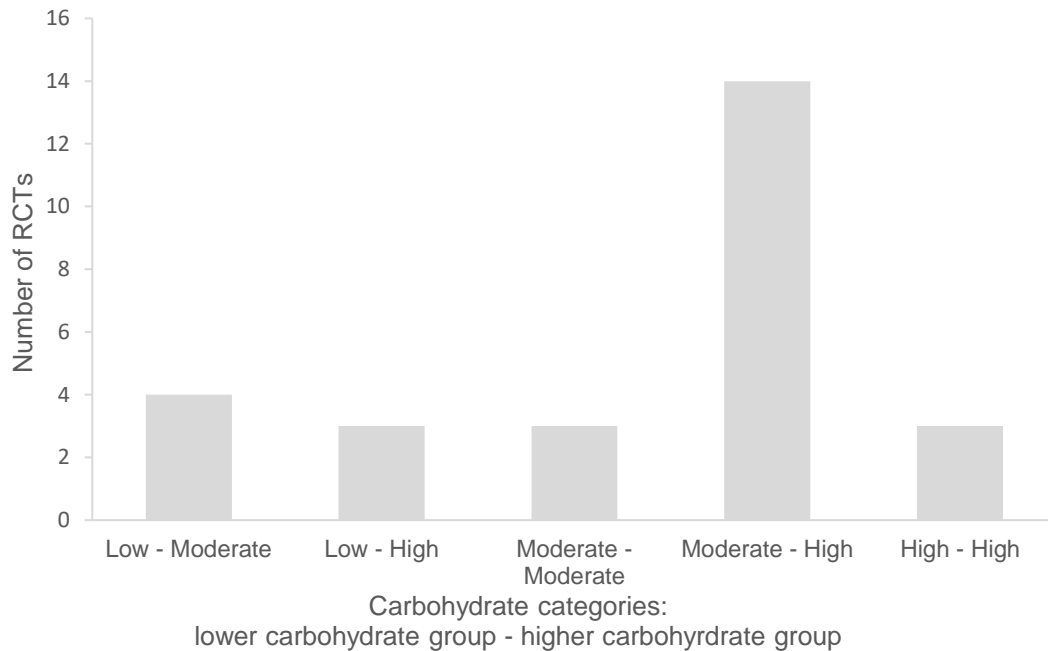[2] Not mean intakes since they are prescribed.
[3] All 13 RCTs reported carbohydrate intake as %TE
[4] Out of 14 RCTs, 10 reported intakes as %TE; 4 reported in g/day and were converted to %TE.
[5] Out of 12 RCTs, 6 reported as g/day; 6 reported in %TE and were converted to g/day.
[6] Out of 13 RCTs, 6 reported intakes in g/day; 7 reported intakes as %TE; and were converted to g/day.

Table 6.3: Prescribed and estimated achieved carbohydrate intakes in primary RCTs included in MAs of 4 prioritised SRs with MAs

SR with MA	Prescribed carbohydrate intakes (% TE) median (range) [category]		Achieved mean carbohydrate intakes (% TE) median (range)* [category]		Comparison of achieved carbohydrate intakes by category (number RCTs)
First author (number RCTs)	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 (17 to 44) [low to moderate]	48 (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 65) [low to high]	39 (13 to 46) [low to high]	49 (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) NR (2)
Sainsbury (2018) (22)	40 (14 to 45) [low to moderate]	55 (23** to 60) [low to high]	36 (13 to 47) [low to high]	50 (41 to 55) [moderate to high]	low vs moderate (2) low vs high (2) moderate vs moderate (3) moderate vs high (10) high vs high (3) NR (2)
van Zuuren (2018) (12)	20 (14 to 40) [low to moderate]	53 (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) NR (3)

Data from RCTs in MAs of 4 prioritised SRs with MAs (reported in 36 publications, see paragraph 6.26); carbohydrate categories in square brackets are based on those proposed by Feinman et al (2015). *Median and range of mean intakes, **1 RCT by Wolever et al (2008) reported prescribed CHO intakes between 20 to 25% TE (possible outlier value). NR, not reported.

Figure 6.1: Comparisons of achieved carbohydrate intakes (% TE) in the lower and higher carbohydrate groups in the primary RCTs according to categories of carbohydrate intake (results for 27 out of 32 RCTs; 5 did not report achieved intakes)

General limitations in the evidence base

6.62 An important limitation in consideration of the evidence was that the 4 prioritised SRs with MAs had different inclusion criteria for cut-offs used to define lower carbohydrate diets (see Table 6.1):

- <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 achieved a lower carbohydrate intake than the control group (Huntriss et al, 2018).

6.63 In addition, van Zuuren et al (2018) only included RCTs that compared lower carbohydrate diets specifically with lower fat (≤30% TE) diets.

6.64 A number of other limitations were identified in the evidence base and were considered as part of the assessment. These are summarised below.

Dietary approach and assessment

6.65 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).

6.66   The majority of primary RCTs were of dietary advice rather than feeding studies so adherence may have been challenging, particularly for participants in the lower carbohydrate groups in the longer-term (≥12 months) RCTs.

6.67   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 clear if misreporting would differ systematically by dietary intervention group.

6.68   Technical difficulties in the dietary assessment process can also affect the accuracy of consumption estimates, such as assumptions made on food composition, recipes and portion sizes.

Carbohydrate intakes

6.69   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 (see Table 5.1) 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 a lower carbohydrate diet in the primary RCTs included in the 4 prioritised SRs with MAs included carbohydrate intakes of up to 50% TE (range, 14 to 50% TE).

6.70   Achieved mean carbohydrate intakes in the lower carbohydrate groups (range, 13 to 47% TE) overlapped with those in the higher carbohydrate groups (range, 41 to 54% TE) (see Table 6.2).

6.71   Categorisation of carbohydrate intakes as *very low*, *low*, *moderate* or *high* is defined as both absolute amounts (g/day) or as percentage of TE (based on an energy intake of 2,000 kcal/day) (see Table 5.1). In some primary studies that included an energy restricted diet, prescribed carbohydrate intakes in the lower carbohydrate group were expressed in grams per day and would be categorised as *low* based on absolute amounts but, since energy intakes were restricted, the amounts consumed would be higher and categorised as *moderate* if expressed as percentage of TE.

6.72   Out of the 27 RCTs that reported estimates of achieved mean carbohydrate intakes, the highest number of comparisons (14 RCTs) were between *moderate* versus *high*; only 3 compared *low* versus *high* intakes.

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

6.74   In order to compensate for reduced carbohydrate intake in the lower carbohydrate groups, the proportions of other macronutrients (usually fats and/or proteins) were increased. However, the potential impact of increasing the proportions of other macronutrients on markers and clinical outcomes of T2D was generally not considered.

6.75   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 dietary composition of these diets was very different in terms of macronutrient composition 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

6.76   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 were taking only oral glucose lowering drugs (no insulin). Several studies provided details of 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.

6.77   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 act alone without the added effect of the medication. In relation to blood lipids, any impact of dietary intervention may have been confounded by pharmaceutical treatment (such as statins) to lower lipids.

Other issues

6.78   The independent effect of weight change on the other measured variables (HbA1c and blood lipid profile) 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 reduction in carbohydrate.

6.79   Primary studies varied in the type of analysis (ITT or PP) used to compare the lower and higher carbohydrate groups (20 RCTs reported ITT analysis, 8 reported PP analysis and 4 did not report type of analysis). 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 lower carbohydrate diets. Although both types of analyses provide useful information, they answer different questions and should be considered separately. However, all MAs combined the results of individual studies regardless of the type of analysis that was used.

6.80   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.

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

Results of MAs in prioritised SRs with MAs and evidence grading

6.82   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.

6.83   All MAs from the 4 prioritised SRs with MAs 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 13 (Tables A13.1 to A13.7).

6.84   The criteria used to grade the evidence are provided in chapter 5 (paragraphs 5.58 to 5.62 and Table 5.3) and summary tables of the grading process for all outcomes are provided in Annex 14 (Tables A14.1 to A14.13).

6.85   Summaries and 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 15 (Table A15.1 to A15.8). The results indicate that both interventions have an effect. They are included to indicate the direction of effect and the absolute changes over time. Results of within-group analyses were not used to grade the evidence.

Primary outcomes

Body weight

6.86   All 4 prioritised SRs with MAs (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. Only results of MAs that included primary RCTs with a minimum follow-up of 12 months were considered in grading the evidence for this outcome.

6.87   The findings from MAs of shorter-term studies (≥3 to <12 months) on body weight that were included in the 4 prioritised SRs with MAs, are briefly described here for interest (the results are provided in Annex 16, Table A16.1). They were not used to grade the evidence since the selection criteria specified that only studies with a minimum duration of 12 months would be considered (see paragraph 5.6, chapter 5); therefore, any SRs and MAs that included only shorter-term (≥3 to <12 months) studies on weight change would have been excluded. As a consequence, the shorter-term results from the 4 prioritised SRs with MAs included here may not be representative of the overall evidence base for shorter-term studies on body weight.

Shorter-term studies (≥3 to <12 months)

6.88   All the shorter-term RCTs included in these MAs had a duration of ≥3 to ≤6 months, except for 1 RCT of 8 months duration.

6.89   Sainsbury et al (2018) conducted separate MAs for weight change at 3 and 6 months, van Zuuren et al (2018) included studies with a duration >16 to 26 weeks (>4 to 6 months) and Korsmo-Haugen et al (2018) included studies of ≥3 to ≤6 months duration. In total, 12 primary RCTs were included in the MAs at 3 months and 17 RCTs were included in MAs at ≥3 to ≤6 months.

6.90   Sainsbury et al (2018) reported a significantly greater weight loss in the lower compared to the higher carbohydrate group at 3 months (WMD -1.08 kg, 95% CI -1.93 to 0.23, p=0.0002, I^2=69%, random-effects model; 12 RCTs, 953 participants) but not at 6 months (WMD -0.14 kg, 95% CI -0.94 to 0.65, p=0.05, I^2=48%, random-effects model; 9 RCTs, 1070 participants).

6.91   van Zuuren et al (2018) reported no difference in weight loss between lower and higher carbohydrate diets (WMD -0.24 kg, 95% CI -1.01 to 0.53, p=0.54, I^2=88%, random-effects model; 7 RCTs, 537 participants).

6.92   Korsmo-Haugen et al (2018) reported 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).

6.93   Huntriss et al (2018) did not perform a MA of shorter-term studies but provided a descriptive analysis. At 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. At 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.

Longer-term studies (≥12 months)

6.94   Korsmo-Haugen et al (2018) reported 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).

6.95   Sainsbury et al (2018) reported 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, 1484 participants, participant numbers in each study were not provided in the forest plots; estimated by the secretariat from table detailing characteristics of primary RCTs). 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, 281 participants) but a significantly greater weight loss with *moderate* compared to the *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, 1203 participants).

6.96   van Zuuren et al (2018) reported 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) were in agreement with the main results.

6.97   Huntriss et al (2018) reported 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).

Summary

6.98   The 2 largest SRs with MAs reporting on change in body weight were Korsmo-Haugen et al (2018) (10 RCTs, n=1163) and Sainsbury et al (2018) (10 RCTs, n=1484). Both reported no significant difference in weight loss between the lower and higher carbohydrate diets in longer-term studies (≥12 months). These results agreed with those from the 2 other MAs (Huntriss et al, 2018; van Zuuren et al, 2018).

6.99   The evidence was graded as *adequate*.

Lower versus higher carbohydrate diets and body weight

Shorter-term studies (≥3 to <12 months)
- Not graded

Longer-term studies (≥12 months)
- No difference in effect
- *Adequate* evidence

HbA1c

6.100   All 4 SRs performed MAs on the effect of a lower versus higher carbohydrate diet on HbA1c. In total, 21 shorter-term (≥3 to <12 months) and 17 longer-term (≥12 months) primary RCTs were included in MAs.

Shorter-term studies (≥3 to <12 months)

6.101   All RCTs included in these MAs measured HbA1c at ≥3 to ≤6 months, except 1 which reported at 8 months (included in MA by Sainsbury et al, 2018 at 6 months).

6.102   Sainsbury et al (2018) conducted separate MAs for HbA1c change in studies of 3 and 6 months duration. The 3-month MA included 1 RCT that reported at 4 months.

6.103   At 3 months, there was a significantly greater reduction in HbA1c concentration in 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, 953 participants).

6.104   Subgroup analyses by prescribed carbohydrate quantity (*low* versus *high* and *moderate* versus *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, 321 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, 632 participants).

6.105   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, 588 participants).

6.106   Results of a sensitivity analysis, removing RCTs at high risk of bias were in agreement with the results of the main analysis with subgroup analysis reporting significantly greater reductions in HbA1c on the *low* versus *high* carbohydrate diet (WMD -0.45% (-4.5 mmol/mol), 95% CI -0.69 to -0.20, p=NR, I^2=NR, random-effects model; 3 RCTs, 237 participants) but not with the *moderate* versus *high* carbohydrate diet (WMD -0.09% (-0.9 mmol/mol), 95% CI -0.24 to 0.06, p=NR, I^2=NR, random-effects model; 5 RCTs, 377 participants).

6.107   At 6 months, there was a significantly greater reduction in HbA1c in 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, 1173 participants).

6.108   Results of a sensitivity analysis excluding RCTs at high risk of bias was in agreement 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, 927 participants).

6.109   A subgroup analysis by carbohydrate quantity reported a significantly greater reduction in HbA1c with a *low* compared to a *high* carbohydrate diet (WMD -0.31% (-3.1 mmol/mol), 95% CI -0.59 to -0.04, p=NR, I^2=NR, random-effects model; 4 RCTs, 244 participants) but not between a *moderate* and a *high* carbohydrate diet (WMD -0.17% (-1.7 mmol/mol, 95% CI -0.42 to 0.09, p=NR, I^2=NR, random-effects model; 4 RCTs, 683 participants).

6.110   van Zuuren et al (2018) (4 to 6 months) reported a significantly greater reduction in HbA1c in 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 were in agreement 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 were in agreement 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).

6.111 Korsmo-Haugen et al (2018) (≥3 to ≤6 months) reported a 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).

6.112 Huntriss et al (2018) did not perform a MA of RCTs with a duration of 3 or 6 months but provided a descriptive analysis.

6.113 At 3 months, 5 out of 7 RCTs reported an average difference of ≥0.2% (-2.0 mmol/mol) favouring the lower carbohydrate diet with 3 of these reporting a difference of ≥0.5% (-5.0 mmol/mol). The remaining 2 RCTs reported no difference between groups. Two 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.

6.114 At 6 months, 7 out of 8 RCTs reported improvement of ≥0.2% (-2.0 mmol/mol) in favour of the lower carbohydrate diet with 3 reporting improvements ≥0.5% (-5.0 mmol/mol). The remaining study reported no difference between groups. Four 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

6.115 At 3 and 6 months, the largest SR with MA was Sainsbury et al (2018) (12 RCTs, n=953 at 3 months and 10 RCTs, n=1173 at 6 months). At both time points there were significantly greater reductions in HbA1c in the lower compared to the higher carbohydrate diet group. These results were in agreement with those of the 2 other MAs (Korsmo-Haugen et al, 2018; van Zuuren et al, 2018).

6.116 The evidence was graded as *adequate*.

Longer-term studies (≥12 months)

6.117 Sainsbury et al (2018) conducted separate MAs for HbA1c change at 12 and 24 months.

6.118 At 12 months, Sainsbury et al (2018) reported 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, 1600 participants).

6.119 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, 335 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, 1265 participants).

6.120   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. In a subgroup analysis based on prescribed carbohydrate quantity, there was 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=NR, I^2=NR, random-effects model; 4 RCTs, 335 participants) or between a *moderate* and *high* carbohydrate diet (WMD -0.13% (-1.3 mmol/mol), 95% CI -0.30 to 0.03, p=NR, I^2=NR, random-effects model; 7 RCTs, 1103 participants).

6.121   At 24 months, there was 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). The results of the MA at 24 months were reported only in the narrative and the RCTs included in the MA were not specified (the included RCTs and number of participants were determined from the table describing characteristics of included studies).

6.122   Korsmo-Haugen et al (2018) reported 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).

6.123   Huntriss et al (2018) reported a 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).

6.124   van Zuuren et al (2018) conducted separate MAs of RCTs with ≥12 months duration and 24 months duration.

6.125   At ≥12 months, van Zuuren et al (2018) reported a 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 were in agreement with the 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).

6.126   At 24 months, there was 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 were in agreement with those of the random-effects model.

Summary

6.127   In longer-term studies with ≥12 months duration, the largest SR with MA (Sainsbury et al, 2018) (12 RCTs, n=1600) reported no difference in HbA1c reduction between the lower and higher carbohydrate diets. These results were in agreement with those of the second largest MA (Korsmo-Haugen et al, 2018) (10 RCTs, n=1030) but in disagreement with results of 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).

6.128   The evidence was graded as *inconsistent* because the results of the largest MA (Sainsbury et al, 2018) (12 RCTs, n=1600) disagreed with those of a sensitivity analysis (excluding 1 RCT at high risk of bias) by Sainsbury et al (2018) and with the 2 other MAs (Huntriss et al, 2018; van Zuuren et al, 2018).

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

6.130   The evidence was graded as *adequate.*

Lower versus higher carbohydrate diets and HbA1c

Shorter-term studies (≥3 to <12 months)
- Greater HbA1c reduction in the lower carbohydrate group
- *Adequate* evidence

Longer-term studies (≥12 to <24 months)
- *Inconsistent* evidence

Longer-term studies (24 months)
- No difference in effect
- *Adequate* evidence

Secondary outcomes

Fasting plasma glucose

6.131 One SR with MA (van Zuuren et al, 2018) examined the difference in effect between lower and higher carbohydrate diets on fasting plasma glucose. In total, 6 shorter-term (≥3 to <12 months) and 4 longer-term (≥12 months) primary RCTs were included in the MAs. van Zuuren et al (2018) also conducted a MA for change in fasting plasma glucose at 24 months but results are not considered here because only 2 RCTs were included (see Table 5.3, chapter 5).

Shorter-term studies (≥3 to <12 months)

6.132 All RCTs included in the MA were of 4 to 6 months duration.

6.133 van Zuuren et al (2018) reported a significantly greater reduction in fasting plasma glucose in the lower compared to the higher carbohydrate diet (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 were in agreement 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).

6.134 A sensitivity analysis excluding RCTs at high risk of bias also reported a significantly greater reduction 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 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

6.135 One SR with MA assessed the effect of a lower compared to a higher carbohydrate diet on fasting plasma glucose (van Zuuren et al, 2018) (6 RCTs, n=396). A significantly greater reduction in fasting plasma glucose was reported in the lower compared to the higher carbohydrate diet in shorter-term studies (≥3 to <12 months).

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

Longer-term studies (≥12 months)

6.137 van Zuuren et al (2018) reported 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).

6.138   A sensitivity analysis excluding studies at high risk of bias, reported no difference in effect between a lower and higher carbohydrate diet (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

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

6.140   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 versus higher carbohydrate diets and fasting plasma glucose

Shorter-term studies (≥3 to <12 months)
- Greater reduction in fasting plasma glucose in the lower carbohydrate group
- *Moderate* evidence

Longer-term studies (≥12 months)
- *Insufficient* evidence

Serum total cholesterol

6.141   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. In total, 4 shorter-term (≥3 to <12 months) and 13 longer-term (≥12 months) primary RCTs were included in MAs.

Shorter-term studies (≥3 to <12 months)

6.142   All RCTs included in the MA by Korsmo-Haugen et al (2018) had a duration of 3 to 6 months.

6.143   Korsmo-Haugen et al (2018) reported 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).

6.144   Huntriss did not conduct a MA of RCTs with a duration of ≥3 to <12 months.

Summary

6.145   One SR with MA (Korsmo-Haugen et al, 2018) (4 RCTs, n=279) assessed the difference in effect between lower and higher carbohydrate diets on serum total cholesterol reduction in shorter-term studies (≥3 to <12 months) and reported no difference.

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

Longer-term studies (≥12 months)

6.147   Korsmo-Haugen et al (2018) reported 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).

6.148   Huntriss et al (2018) reported 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

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

6.150   The evidence was graded as *adequate*.

Lower versus higher carbohydrate diets and serum total cholesterol

Shorter-term studies (≥3 to <12 months)
- No difference in effect
- *Moderate* evidence

Longer-term studies (≥12 months)
- No difference in effect
- *Adequate* evidence

Serum triacylglycerol

6.151   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. In total, 12 shorter-term (≥3 to <12 months) and 13 longer-term (≥12 months) primary RCTs were included in MAs.

6.152   van Zuuren et al (2018) also conducted a MA for change in serum triacylglycerol at 24 months but results are not considered here because only 2 RCTs were included (see Table 5.3, chapter 5).

Shorter-term studies (≥3 to <12 months)

6.153   All the shorter-term (≥3 to <12 months) RCTs included in MAs had a duration of 3 to 6 months.

6.154   Korsmo-Haugen et al (2018) reported a greater reduction in serum triacylglycerol with a lower compared to a higher carbohydrate diet 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).

6.155   van Zuuren et al (2018) reported a significantly greater reduction in serum triacylglycerol with a lower compared to a higher carbohydrate diet (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 were in agreement 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).

6.156   Huntriss did not conduct a MA of RCTs with a duration of ≥3 to <12 months.

Summary

6.157   The largest SR with MA (van Zuuren et al, 2018) (6 RCTs, n=508) reported a significantly greater reduction in serum triacylglycerol in the lower compared to the higher carbohydrate diet in shorter-term studies (≥3 to <12 months). This was consistent with the results of the MA by Korsmo-Haugen et al (2018) but significance was not reported (and upper confidence interval was 0).

6.158   The evidence was graded as *adequate*.

Longer-term studies (≥12 months)

6.159   Korsmo-Haugen et al (2018) reported 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).

6.160   Huntriss et al (2018) reported a significantly greater reduction in serum triacylglycerol with the lower compared to the higher carbohydrate diets on reduction in serum triacylglycerol (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).

6.161   van Zuuren et al (2018) reported a significantly greater reduction in serum triacylglycerol with a lower compared to a higher carbohydrate diet (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 a lower compared to a higher carbohydrate diet (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

6.162   The largest SR with MA (Korsmo-Haugen et al, 2018) (9 RCTs, n=967) reported no difference between lower and higher carbohydrate diets on serum triacylglycerol reduction in longer-term studies (≥12 months). These results disagreed with those 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 a lower compared to a higher carbohydrate diet.

6.163   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 other 2 MAs (Huntriss et al, 2018) (7 RCTs, n=645) (van Zuuren et al, 2018) (5 RCTs, n=468).

Lower versus higher carbohydrate diets and serum triacylglycerol

Shorter-term studies (≥3 to <12 months)
- Greater reduction in serum triacylglycerol in the lower carbohydrate group
- *Adequate* evidence

Longer-term studies (≥12 months)
- *Inconsistent* evidence

Serum LDL cholesterol

6.164   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. In total, 10 shorter-term (≥3 to <12 months) and 11 longer-term (≥12 months) primary RCTs were included in MAs.

Shorter-term studies (≥3 to <12 months)

6.165   All the shorter-term (≥3 to <12 months) RCTs had a duration of 3 to 6 months.

6.166   Korsmo-Haugen et al (2018) reported 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).

6.167   van Zuuren et al (2018) reported 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.

6.168   Huntriss did not conduct a MA of RCTs with a duration of ≥3 to <12 months.

Summary

6.169   The MA with the largest number of participants (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 shorter-term studies (≥3 to <12 months). This agreed with results of the other MA (Korsmo-Haugen et al, 2018) (6 RCTs, n=345).

6.170   The evidence was graded as *adequate*.

Longer-term studies (≥12 months)

6.171   Korsmo-Haugen et al (2018) reported 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).

6.172   Huntriss et al (2018) reported 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).

6.173   van Zuuren et al (2018) reported 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

6.174   The largest SR with MA (Korsmo-Haugen et al, 2018) (9 RCTs, n=1064) reported no difference in effect between the lower and higher carbohydrate diets on change in serum LDL cholesterol in longer-term studies (≥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).

6.175   The evidence was graded as *adequate*.

Lower versus higher carbohydrate diets and serum LDL cholesterol

Shorter-term studies (≥3 to <12 months)
- No difference in effect
- *Adequate* evidence

Longer-term studies (≥12 months)
- No difference in effect
- *Adequate* evidence

Serum HDL cholesterol

6.176   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. In total, 11 shorter-term (≥3 to <12 months) and 13 longer-term (≥12 months) primary RCTs were included in MAs.

6.177   van Zuuren et al (2018) also conducted a MA for change in serum HDL cholesterol at 24 months but results are not considered here because only 2 RCTs were included (see Table 5.3, chapter 5).

Shorter-term studies (≥3 to <12 months)

6.178   All the shorter-term (≥3 to <12 months) RCTs had a duration of 3 to 6 months.

6.179   van Zuuren et al (2018) reported no difference 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 were in agreement

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 the lower compared to the higher carbohydrate diet (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).

6.180   Korsmo-Haugen et al (2018) reported 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).

6.181   Huntriss did not conduct a MA of RCTs with a duration of ≥3 to <12 months.

Summary

6.182   The largest SR with MA (van Zuuren et al, 2018) (6 RCTs, n=508) reported no difference in effect between the lower and higher carbohydrate diets in serum HDL cholesterol in shorter-term studies (≥3 to <12 months). This agreed with results from the other SR with MA (Korsmo-Haugen et al, 2018) (6 RCTs, n=345) but disagreed with the results of a sensitivity analysis excluding RCTs causing substantial heterogeneity (van Zuuren et al, 2018).

6.183   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 studies (≥12 months)

6.184   Korsmo-Haugen et al (2018) reported no difference in effect between lower and higher carbohydrate diets on increasing 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).

6.185   Huntriss et al (2018) reported a significantly greater increase in serum HDL cholesterol with the lower compared to the higher carbohydrate diet (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).

6.186   van Zuuren et al (2018) reported a significantly greater increase in serum HDL cholesterol with the lower compared to the higher carbohydrate diet (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 studies at high risk of bias (1 RCT) also reported a significantly greater increase in serum HDL cholesterol in the lower compared

to the higher carbohydrate diet (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

6.187   The largest SR with MA (Korsmo-Haugen et al, 2018) (10 RCTs, n=1093) reported no difference in effect between the lower and higher carbohydrate diets on serum HDL cholesterol in longer-term studies (≥12 months). This disagreed with results of the 2 other SRs with 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).

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

Lower versus higher carbohydrate diets and serum HDL cholesterol

---

Shorter-term studies (≥3 to <12 months)
- *Inconsistent* evidence

Longer-term studies (≥12 months)
- *Inconsistent* evidence

Serum total cholesterol:HDL cholesterol ratio

6.189   None of the SRs with MAs considered serum total cholesterol:HDL cholesterol ratio as an outcome.

Medication use and diabetes-related symptoms

6.190   None of the 4 prioritised SRs with MAs considered diabetes-related symptoms as an outcome.

6.191   Only 1 SR (Huntriss et al, 2018) assessed change in diabetes medication use as an outcome but provided a narrative synthesis only (see paragraphs 6.192 to 6.194 below). Observations on medication use from the 3 other SRs with MAs are summarised in Annex 12 (Table A12.2).

6.192   Huntriss et al, (2018) reported that out of the 18 RCTs (n=2204) in the SR, 16 included participants on diabetes medication at trial start; 2 of these did not report on medication changes. Out of the remaining 14 RCTs, 6 reported medication changes in the shorter term (≥3 to <12 months) and 8 reported medication changes in the longer term (≥12 months).

Shorter-term studies (≥3 to <12 months)

6.193   Out of 6 RCTs that reported medication changes in the shorter term (≥3 to <12 months), 5 reported a significant reduction in diabetes medication in the lower carbohydrate diet group (p≤0.05).

Longer-term studies (≥12 months)

6.194   Out of the 8 RCTs that reported medication changes in the longer term (≥12 months), 4 reported a significant reduction in diabetes medication in the lower carbohydrate group (p≤0.05).

Summary

6.195   One SR (Huntriss et al, 2018) assessed medication change as an outcome, providing a narrative synthesis only.

6.196   Five out of 6 shorter-term studies (≥3 to <12 months) reported a significant reduction in diabetes medication in the lower carbohydrate group (p≤0.05).

6.197   Four out of 8 longer-term (≥12 months) RCTs reported a significant reduction in diabetes medication in the lower carbohydrate group (p≤0.05).

6.198   This outcome was not graded because a MA was not performed.

Summary of evidence grading for all outcomes

6.199   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 between groups in effect) is summarised in Table 6.4.

Table 6.4: Summary of strength of the evidence from RCTs on effects of lower versus higher carbohydrate diets on primary and secondary outcomes of T2D

Outcome	Shorter-term studies (3 to ≤12m)		Longer-term studies (≥12m)	
	Difference in effect	Strength of evidence	Difference in effect	Strength of evidence
Primary				
Body weight	Not graded (only longer-term weight change graded)		—	Adequate
HbA1c	↓	Adequate	Inconsistent (≥12 to <24 months)	
			—	Adequate (24 months)
Secondary				
Fasting plasma glucose	↓	Moderate	Insufficient	
Serum total cholesterol	—	Moderate	—	Adequate
Serum triacylglycerol	↓	Adequate	Inconsistent	
Serum LDL cholesterol	—	Adequate	—	Adequate
Serum HDL cholesterol	Inconsistent		Inconsistent	
Serum TC:HDL ratio	No evidence: none of the 4 prioritised SRs with MAs included this outcome			
Medication use and diabetes-related symptoms	No evidence: None of the 4 prioritised SRs with MAs performed MA of medication use; 1 included diabetes medication use as an outcome but only provided a narrative synthesis. None of the 4 prioritised SRs with MAs considered diabetes-related symptoms as an outcome.			

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

Adverse events

SRs with MAs

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

6.201   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.

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

6.203   All 4 SRs with MAs observed the potential of carbohydrate-restricted diets to detrimentally impact CVD risk markers.

Primary RCTs

6.204   Thirteen of the primary RCTs included in the 4 SRs with MAs reported on adverse events that occurred during the study (see Annex 17, Table A17.1). Out of these, none reported any serious adverse events related to the diet. The most common adverse events experienced during the study included gastroenteritis, nausea, vomiting and headaches.

6.205   There were no significant differences between the lower and higher carbohydrate groups in reported adverse events except in 1 RCT (Goday et al, 2016) that prescribed *very low* carbohydrate intakes (<50g/day): adverse events were reported by 80% of participants in the *very low* carbohydrate group compared to 41% in the higher carbohydrate group (p<0.001). Headache, nausea and vomiting were more common in the *very low* carbohydrate group at 2 weeks (all p<0.05). At the end of the study, constipation (p<0.005) and orthostatic hypotension (p<0.05) were more common in the *very low* carbohydrate group compared with the higher carbohydrate group.

Potential long-term concerns

6.206   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 studies.

6.207   The reduced carbohydrate intake in lower carbohydrate diets is usually replaced by increased consumption of protein or fat. In the primary RCTs, total and saturated fat intakes were above government recommendations in the lower carbohydrate diets. This is a potential concern since long-term higher consumption of saturated fats increases CVD risk (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.

6.208   Another potential concern is that lower carbohydrate diets could lead to a reduction in fibre and essential micronutrient intake as a result of restricted intakes of cereals, grains and some types of fruit and vegetables (Churuangsuk et al, 2019).

Summary

6.209   Evidence from the primary RCTs included in the SR with MAs suggests little difference in adverse events between lower and higher carbohydrate diets in the short term.

6.210   Limited evidence suggests *very low* carbohydrate (20 to 50 g/day; <10% TE) diets are associated with some adverse events (headache, nausea, vomiting, constipation, hypotension).

6.211   The implications of longer-term consumption of lower carbohydrate diets in adults with T2D are unknown.

7 Overall summary and conclusions

Summary

7.1 This report reviews the evidence on lower carbohydrate diets compared to current UK government advice for adults with T2D.

Terms of reference

7.2 These 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

7.3 The report is based on evidence provided by SRs with MAs of RCTs.

7.4 The primary outcomes considered were body weight and HbA1c. Secondary outcomes were: fasting plasma glucose, blood lipid profiles (serum total cholesterol; serum triacylglycerol; serum LDL cholesterol; serum HDL cholesterol; serum total cholesterol:HDL cholesterol ratio); and changes in medication and diabetes-related symptoms.

7.5 All outcomes were assessed in the shorter term (defined as ≥3 to <12 months) and longer term (defined as ≥12 months) except for body weight, where only longer-term studies (reflecting maintenance of weight loss) were considered. Although shorter-term study duration was defined as ≥3 to <12 months, all except one of the primary studies included in the identified SRs considered outcomes between 3 and 6 months. Out of the longer-term studies (≥12 months) only 7 had a duration beyond 12 months.

7.6 Eight SRs with MAs and 1 network meta-analysis (NMA) were considered eligible for inclusion in the evidence review. Information was extracted from the primary RCTs (n=44) included in the 8 SRs with MAs to inform a detailed assessment of the data, including: reported intakes of macronutrients (carbohydrates, fats and protein) and energy in the lower and higher carbohydrate groups; medication use; type of analysis; loss to follow-up; and physical activity.

7.7 Results from the 4 most recent 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. Only 1 primary RCT that was included in the non-prioritised SRs with MAs was not covered by the 4 prioritised SRs with MAs. In total, 32 RCTs were included in the MAs of the 4 prioritised SRs with MAs.

7.8 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.

Definition of diets containing different amounts of carbohydrates

7.9 There is no agreed definition of a low carbohydrate diet. To allow comparisons of carbohydrate intakes across the primary studies, the following categories were adopted to group carbohydrate intakes (g/day or % TE) as *very low, low, moderate* and *high* (see Table 7.1).

Table 7.1: Categories of dietary carbohydrate intakes*

Description	Amount of carbohydrate	
	g/day	% TE (based on 2000 kcal/day)
Very low carbohydrate∞	20 to 50	≤10
Low carbohydrate	>50 to <130	>10 to <26
Moderate carbohydrate	130 to 230	26 to 45
High carbohydrate	>230	>45

*Based on Feinman et al (2015) and Accurso et al (2008)
∞Also referred to as ketogenic diets.

7.10 Based on these categories, government recommendations on carbohydrate intake for the general population (50% TE) would be classified as *high.*

7.11 Comparisons in this report were between lower and higher carbohydrate diets because definitions of low and high carbohydrate intakes varied across studies.

Macronutrient and energy intakes in the primary RCTs

Carbohydrate intakes

7.12 Prescribed carbohydrate intakes ranged from 14 to 50% TE in the lower carbohydrate groups and 23 to 65% TE in the higher carbohydrate groups. According to categories of carbohydrate intakes, prescribed intakes ranged from *low* to *high* in both lower and higher carbohydrate groups.

7.13   In shorter-term (≥3 to <12 months) studies, reported achieved mean carbohydrate intakes ranged from 13 to 47% TE in the lower carbohydrate groups and 41 to 55% TE in the higher carbohydrate groups. According to categories of carbohydrate intakes, achieved mean intakes ranged from *low* to *high* in the lower carbohydrate groups and *moderate* to *high* in the higher carbohydrate groups*.*

7.14   In longer-term (≥12 months) studies, reported achieved mean carbohydrate intakes ranged from 18 to 46% TE in the lower carbohydrate groups and 43 to 54% TE in the higher carbohydrate groups. According to categories of carbohydrate intakes, achieved mean intakes ranged from *low* to *high* in the lower carbohydrate groups and *moderate* to *high* in the higher carbohydrate groups.

Fat intakes

7.15   In shorter-term (≥3 to <12 months) studies, estimated 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. Estimated mean intake ranges of SFA, PUFA and MUFA were:

- SFA – 6 to 20% TE in the lower carbohydrate groups and 8 to 12% TE in the higher carbohydrate groups.
- PUFA - 4 to 9% TE in the lower carbohydrate groups and 5 to 7% TE in the higher carbohydrate groups.
- MUFA - 8 to 17% TE in the lower carbohydrate groups and 10 to 12% TE in the higher carbohydrate groups.

7.16   In longer-term (≥12 months) studies, estimated mean intakes of total fats ranged from 31 to 58% TE in the lower carbohydrate groups and 27 to 40% TE in the higher carbohydrate groups. Estimated mean intake ranges of SFA, PUFA and MUFA were:

- SFA - 10 to 19% TE in the lower carbohydrate groups and 8 to 13% TE in the higher carbohydrate groups.

- PUFA - 6 to 13% TE in the lower carbohydrate groups and 4 to 7% TE in the higher carbohydrate groups.

- MUFA - 13 to 25% TE in the lower carbohydrate groups and 11 to 13% TE in the higher carbohydrate groups.

Protein intakes

7.17   In shorter-term (≥3 to <12 months) studies, estimated mean protein intakes ranged from 19 to 37% TE in the lower carbohydrate groups and 16 to 23% TE in the higher carbohydrate groups.

7.18   In longer-term (≥12 months) studies, estimated achieved 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

7.19　In shorter-term (≥3 to <12 months) studies, estimated mean energy intakes ranged from 1,273 to 2,029 kcal (5,326 to 8,489 kJ/day) (median, 1,557 kcal/day; 6,514 kJ/day) in the lower carbohydrate groups and 1,197 to 1,785 kcal/day (5,008 to 7,468 kJ/day) (median, 1,522 kcal/day; 6,368 kJ/day) in the higher carbohydrate groups.

7.20　In longer-term (≥12 months) studies, estimated mean energy intakes ranged from 1,251 to 2,222 kcal/day (5,234 to 9,297 kJ/day) (median, 1,708 kcal/day; 7,146 kJ/day) in the lower carbohydrate groups and 1,420 to 2,222 kcal/day (5,941 to 9,297 kJ/day) (median, 1,757 kcal/day; 7,351 kJ/day) in the higher carbohydrate groups.

Limitations in the evidence base

7.21　There were several limitations in the quality of the evidence base.

7.22　One of the most important limitations was the lack of an agreed definition for a low carbohydrate diet. In the 4 prioritised SRs with MAs that were considered in evaluating and grading the evidence, the cut-offs for defining a low carbohydrate diet varied: ≤40% TE (2 SRs), ≤45% TE (1 SR), no specific cut-off, the lower carbohydrate groups must have achieved lower intakes than the comparator groups (1 SR).

7.23　In the primary RCTs included in the MAs of the 4 prioritised SRs with MAs, there was considerable overlap between prescribed carbohydrate intakes in the lower (14 to 50% TE) and higher (23 to 65% TE) carbohydrate groups.

7.24　Estimated mean achieved carbohydrate intakes in the lower carbohydrate groups ranged between 13 to 47% TE and, in most studies, were above the definition of a *low* carbohydrate diet according to categories of carbohydrate intake (>10 to <26% TE or >50 to <130 g/day).

7.25　Out of 27 RCTs that reported achieved mean intakes of carbohydrates, the highest number of comparisons (14 RCTs) were between *moderate* versus *high* carbohydrate intakes; only 3 RCTs compared *low* versus *high* carbohydrate intakes.

7.26　As well as being very heterogeneous in the amounts of carbohydrates prescribed and achieved in the *lower* carbohydrate categories, the primary RCTs varied in the type and amount of macronutrient that replaced carbohydrate (usually fat and/or protein) and in the duration and intensity of the advice given to participants in how to follow their prescribed diets. Very few trials included details on the type of carbohydrate consumed (for example, those with differing free sugar or fibre content, wholegrain versus refined) or considered how this could affect the outcomes under consideration.

7.27   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 one of the primary outcomes under consideration (HbA1c) since reducing medication in the lower carbohydrate group could reduce differences in HbA1c change between the intervention groups.

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

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

Evidence grading

Primary outcomes

Body weight

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

HbA1c

7.31   There was *adequate* evidence from RCTs of a greater reduction in HbA1c with lower compared to higher carbohydrate diets in the shorter term (≥3 to <12 months).

7.32   The evidence was graded as *inconsistent* in the longer term (≥12 to <24 months) because of disagreement with other publications and with the results of a sensitivity analysis (after removal of 1 RCT at high risk of bias).

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

Secondary outcomes

Fasting plasma glucose

7.34   There was *moderate* evidence from RCTs of a greater reduction in fasting plasma glucose with the lower compared to the higher carbohydrate diets in the

shorter term (≥3 to <12 months). The evidence was graded as *moderate* because only 1 MA (n=396), which compared lower carbohydrate diets specifically with low fat (<30% TE) diets, assessed this outcome. The MA also included 1 non-randomised trial.

7.35   There was *insufficient* evidence from RCTs to assess if there was a difference between lower and higher carbohydrate diets on reducing fasting plasma glucose in the longer term (≥12 months). The evidence was graded as *insufficient* because there was only 1 MA with very high heterogeneity (92%).

Serum total cholesterol

7.36   There was *moderate* evidence from RCTs for no difference in effect between lower and higher carbohydrate diets in reducing serum total cholesterol in the shorter term (≥3 to <12 months). The evidence was graded as *moderate* because only 1 MA with a small sample size (n=279) considered this outcome.

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

Serum triacylglycerol

7.38   There was *adequate* evidence from RCTs of a greater reduction in serum triacylglycerol with lower compared to higher carbohydrate diets in the shorter term (≥3 to <12 months).

7.39   The evidence was graded as *inconsistent* in longer-term RCTs (≥12 months) because of disagreement between the MAs.

Serum LDL cholesterol

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

Serum HDL cholesterol

7.41   The evidence on lower compared to higher carbohydrate diets on serum HDL cholesterol was *inconsistent* in shorter-term RCTs (≥3 to <12 months). The evidence was graded as *inconsistent* because of disagreement with the results of a sensitivity analysis excluding RCTs causing substantial heterogeneity.

7.42   The evidence was graded as *inconsistent* in longer-term RCTs (≥12 months) because of disagreement between MAs.

Serum total cholesterol:HDL cholesterol ratio

7.43   None of the SRs with MAs considered serum total cholesterol:HDL cholesterol ratio as an outcome.

Medication use and diabetes-related symptoms

7.44   The evidence for this outcome was not graded because a MA was not performed.

7.45   One SR assessed medication change as an outcome but only provided a narrative synthesis and reported specifically on diabetes medication. Five out of 6 shorter-term RCTs reported a significant reduction in diabetes medication in the lower carbohydrate diet group. Four out of 8 longer-term RCTs reported a significant reduction in diabetes medication in the lower carbohydrate diet group.

7.46   None of the SRs with MAs considered changes in diabetes-related symptoms as an outcome.

Table 7.2: Summary of strength of the evidence from RCTs on effects of lower versus higher carbohydrate diets on primary and secondary outcomes of T2D

Outcome	Shorter-term studies (3 to ≤12m)		Longer-term studies (≥12m)	
	Difference in effect	Strength of evidence	Difference in effect	Strength of evidence
Primary				
Body weight	Not graded (only longer-term weight change graded)		—	Adequate
HbA1c	↓	Adequate	Inconsistent (≥12 to <24 months)	
			—	Adequate (24 months)
Secondary				
Fasting plasma glucose	↓	Moderate	Insufficient	
Serum total cholesterol	—	Moderate	—	Adequate
Serum triacylglycerol	↓	Adequate	Inconsistent	
Serum LDL cholesterol	—	Adequate	—	Adequate
Serum HDL cholesterol	Inconsistent		Inconsistent	
Serum TC:HDL ratio	No evidence: none of the 4 prioritised SRs with MAs included this outcome			
Medication use and diabetes-related symptoms	No evidence: None of the 4 prioritised SRs with MAs performed MA of medication use; 1 included diabetes medication use as an outcome but only provided a narrative synthesis. None of the 4 prioritised SRs with MAs considered diabetes-related symptoms as an outcome.			

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

Adverse events

7.47   Studies did not identify any harmful effects of lower carbohydrate intakes in the short-term.

7.48   Total and SFA intakes were above government recommendations in the lower carbohydrate diets compared with higher carbohydrate diets. This is a potential concern in the long term since high saturated fat intakes increase CVD risk (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.

7.49   Another potential concern is that lower carbohydrate diets could lead to reduced intakes of essential micronutrients and fibre as a result of restricted intakes of grains, fruits and vegetables.

Conclusions

7.50   The terms of reference for this review were to consider the impact of lower carbohydrate diets compared to current government advice on carbohydrate intake (about 50% TE) on markers and clinical outcomes of T2D in adults with T2D.

7.51   The primary outcomes selected for consideration were body weight and HbA1c; secondary outcomes were fasting plasma glucose, blood lipid profiles and changes in medication and diabetes-related symptoms. All outcomes were assessed in the shorter term (defined as ≥3 to <12 months) and longer term (defined as ≥12 months) except for body weight, where only longer-term studies were considered. Although shorter-term study duration was defined as ≥3 to <12 months, all except one of the primary studies included in the prioritised SRs considered outcomes between 3 and 6 months. Out of the longer-term primary studies (defined as ≥12 months), only 7 had a duration above 12 months.

7.52   There is no universally agreed definition of a low carbohydrate diet. For the purposes of this review, the following categories were adopted to enable comparison across studies: *very low* (20 to 50 g/day or ≤10% TE), *low* (>50 to <130 g/day or >10 to <26% TE), *moderate* (130 to 230 g/day or 26 to 45% TE), *high* (>230 g/day or >45% TE). According to these categories, current UK government advice on carbohydrate intake would be considered *high*.

7.53 In considering the evidence, 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 the lower carbohydrate group ranging from 14 to 50% TE (median, 40% TE)

- estimated mean achieved carbohydrate intakes reported in the lower carbohydrate groups ranged between 13 to 47% TE but were *moderate* (26 to 45% TE) in the majority of primary RCTs.

7.54 Comparisons were, therefore, mainly between the impact of lower and higher carbohydrate diets. This limits the interpretation of the evidence for any benefits or harms of a 'low' compared to a 'high' carbohydrate diet.

7.55 The evidence considered for the following markers and clinical outcomes of T2D suggests that for adults with T2D:

- body weight — no difference between lower and higher carbohydrate diets in the longer term (shorter-term weight changes were not considered)

- HbA1c — lower carbohydrate diets have benefits over higher carbohydrate diets in the shorter term but evidence for longer-term effects are unclear

- fasting plasma glucose — lower carbohydrate diets have benefits over higher carbohydrate diets in the shorter term but there is insufficient evidence to assess longer-term effects

- serum total cholesterol — no difference between lower and higher carbohydrate diets in the shorter or longer term

- serum triacylglycerol — lower carbohydrate diets have benefits over higher carbohydrate diets in the shorter term but evidence for longer-term effects are inconsistent

- serum LDL cholesterol — no difference between lower and higher carbohydrate diets in the shorter term or longer term

- serum HDL cholesterol — evidence for shorter-term and longer-term effects is inconsistent

- serum total cholesterol:HDL cholesterol ratio — none of the SRs with MAs considered this outcome

- medication use — lower carbohydrate diets may have a beneficial effect in reducing diabetes medication but the evidence is unclear because of inconsistencies in the reporting and measurement of diabetes medications across primary studies

- diabetes-related symptoms — none of the SRs with MAs considered this outcome.

7.56   Overall, the evidence suggests beneficial effects of lower carbohydrate diets for some outcomes (HbA1c, fasting plasma glucose, serum triacylglycerol) in the shorter term which are unclear in the longer term. No differences were observed between higher and lower carbohydrate diets on body weight in the longer term (shorter term changes were not considered) or on serum total cholesterol, serum LDL cholesterol and serum HDL cholesterol either in the shorter term or longer term.

7.57   These findings need to be interpreted with caution since weight loss was a primary outcome in many of the primary RCTs. 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 reduction in carbohydrate.

7.58   In relation to blood lipid profiles, it is difficult to separate the effects of diet and effects of weight loss from effects of lipid-lowering medication (such as statins) since many participants were taking such medications.

7.59   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; differences in achieved carbohydrate intakes between lower and higher carbohydrate diets were often smaller than prescribed; and inherent inaccuracies in estimates of dietary intake.

7.60   An important limitation in the evidence base was that few studies assessed outcomes beyond 12 months.

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

7.62   This report did not assess 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.

7.63   In general, no adverse events were reported with lower carbohydrate diets, but study duration did not extend beyond 12 months in the majority of primary RCTs. The effect of lower carbohydrate diets over several years in adults with T2D are unknown.

7.64   Several gaps were identified in the evidence base. No trials provided information about the type of carbohydrate consumed (for example, those with differing free sugar or fibre content, wholegrains compared to refined starch) or considered how this could affect the outcomes of interest. In addition, few trials assessed longer-term effects (beyond 12 months) of lower carbohydrate diets, and none considered hard endpoints such as diabetes complications, CVD events or mortality.

8 Recommendations

To be added post-consultation

9 Research recommendations

To be added post-consultation

10 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.
Clinical controlled trial (CCT)	A study design based in a clinic 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/ disease.
Ketogenic diet	A low-carbohydrate eating regime in order to promote the 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.
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 saturated fat is a fat that has as many hydrogen atoms as they can hold (that is, they are '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.

11 References

Accurso A, Bernstein RK, Dahlqvist A, Draznin B, Feinman RD, Fine EJ, et al (2008) Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. Nutr Metab. 5:9.

ADA (2019a) Classification and diagnosis of diabetes: standards of medical care in diabetes - 2019. Diabetes Care.S13-S28.

ADA (2019b) Lifestyle management: standards of medical care in diabetes - 2019. Diabetes Care. 42(1):S46-S60.

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). American Journal of Clinical Nutrition. 97(3):505-516.

AMSTAR (2017) AMSTAR 2. Available from: https://amstar.ca/Amstar-2.php

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.

Athinarayanan SJ, Adams RN, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW, et al (2019) Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Non-randomized Clinical Trial. Front Endocrinol. 10:348.

Bates BL, A; Prentice, A; Bates, C; Page, P; Nicholson, S; Swan, G (2014) National Diet and Nutrition Suvery: Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 - 2011/2012) Available from: https://bit.ly/30lr2qj

Bhanpuri NH, Hallberg SJ, Williams PT, McKenzie AL, Ballard KD, Campbell WW, et al (2018) Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study. Cardiovasc Diabetol. 17(1):56.

Brinkworth GD, Noakes M, Parker B, Foster P & Clifton PM (2004) Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with type 2 diabetes: one-year follow-up of a randomised trial. Diabetologia. 47(10):1677-1686.

Brouns F, Bjorck I, Frayn KN, Gibbs AL, Lang V, Slama G, et al (2005) Glycaemic index methodology. Nutr Res Rev. 18(1):145-171.

Byrne C, Caskey F, Castledine C, Davenport A, Dawnay A, Fraser S, et al (2018) UK Renal Registry 20th Annual Report of the Renal Association. Available from: https://bit.ly/36DnDW3

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(6):1270-1276.

Churuangsuk C, Griffiths D, Lean MEJ & Combet E (2019) Impacts of carbohydrate-restricted diets on micronutrient intakes and status: A systematic review. Obes Rev. 20(8):1132-1147.

Codex Alimentarius (1995) Codex standard for formula foods for use in very low energy diets for weight reduction Available from: https://bit.ly/2LOOINI

Diabetes Australia (2015) Eating well. Available from: https://www.diabetesaustralia.com.au/eating-well

Diabetes Australia (2018) Position statement: low carbohydrate eating for people with diabetes. Available from: https://bit.ly/38yMD27

Diabetes UK (2018a) Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. Available from: https://bit.ly/2PIbkk6

Diabetes UK (2018b) Diabetes UK interim position statement on remission in adults with Type 2 diabetes. Available from: https://bit.ly/38wI0Wr

Diabetes UK (2018c) Diabetes UK position on prevention of Type 2 diabetes: whole-society inteventions to reduce obesity. Available from: https://bit.ly/2LOa1Pt

Diabetes UK (2019) Us, diabetes and a lot of facts and stats. Available from: https://bit.ly/2RKhcfy

Elia M & Cummings JH (2007) Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates. Eur J Clin Nutr. 61 Suppl 1:S40-74.

Facchini FS & Saylor KL (2003) A low-iron-available, polyphenol-enriched, carbohydrate-restricted diet to slow progression of diabetic nephropathy. Diabetes. 52(5):1204-1209.

Fan Y, Di H, Chen G, Mao X & Liu C (2016) Effects of low carbohydrate diets in individuals with type 2 diabetes: Systematic review and meta-analysis. Int J Clin Exp Med. 9(6):11166-11174.

FAO/WHO (1998) Carbohydrates in human nutrition. Available from: http://www.fao.org/3/W8079E/w8079e00.htm#Contents

Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al (2015) Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 31(1):1-13.

Garg A (1998) High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr. 67(3 Suppl):577S-582S.

Guldbrand H, Dizdar B, Bunjaku B, Lindstrom T, Bachrach-Lindstrom M, Fredrikson M, et al (2012) In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 55(8):2118-2127.

Hallberg SJ, McKenzie AL, Williams PT, Bhanpuri NH, Peters AL, Campbell WW, et al (2018) Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. Diabetes Ther. 9(2):583-612.

Hauner H (2010) Obesity and diabetes. In: Holt RIG, Cockram CS, Flyvbjerg A, et al, editors. Textbook of diabetes. 4th ed. Oxford: Wiley-Blackwell.

Hawksworth G, Drasar BS & Hill MJ (1971) Intestinal bacteria and the hydrolysis of glycosidic bonds. J Med Microbiol. 4(4):451-459.

Huntriss R, Campbell M & Bedwell C (2018) The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr. 72(3):311-325.

Iqbal N, Vetter ML, Moore RH, Chittams JL, Dalton-Bakes CV, Dowd M, et al (2010) Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. Obesity 18(9):1733-1738.

Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, et al (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 34(3):362-366.

Jonasson L, Guldbrand H, Lundberg AK & Nystrom FH (2014) Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann Med. 46(3):182-187.

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.

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.

Korsmo-Haugen H-K, Brurberg KG, Mann J & Aas A-M (2018) Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab.1-13.

Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al (2019) Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 7(5):344-355.

Mann JI, De Leeuw I, Hermansen K, Karamanos B, Karlstrom B, Katsilambros N, et al (2004) Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis. 14(6):373-394.

McArdle PD, Greenfield SM, Rilstone SK, Narendran P, Haque MS & Gill PS (2018) Carbohydrate restriction for glycaemic control in Type 2 diabetes: a systematic review and meta-analysis. Diabet Med.

Meng Y, Bai H, Wang S, Li Z, Wang Q & Chen L (2017) Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 131:124-131.

Miller BM & Brennan L (2015) Measuring and reporting attrition from obesity treatment programs: A call to action! Obes Res Clin Pract. 9(3):187-202.

Naude CE, Schoonees A, Senekal M, Young T, Garner P & Volmink J (2014) Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis. PLoS One. 9(7):e100652.

NCVIN (2018) Diabetes Foot Care Profiles 2014-2017. Available from: https://fingertips.phe.org.uk/profile/diabetes-ft

NGSP (2010) IFCC standardization of HbA1c. Available from: http://www.ngsp.org/ifccngsp.asp

NHS Digital (2017) National Diabetes Audit Complications and Mortality 2015-2016. Available from: https://bit.ly/36poEkj

NHS Digital (2018) National Diabetes Audit - Report 1 Care processes and treatment targets 2017-18. Available from: https://bit.ly/2E997Jf

NHS Scotland (2018) Scottish Diabetes Survey 2017. Available from: http://www.diabetesinscotland.org.uk/Publications/SDS%202017.pdf

NICE (2014) Obesity: identification, assessment and management [CG189]. Available from: https://www.nice.org.uk/guidance/cg189

NICE (2017) Type 2 diabetes: prevention in people at high risk [PH38]. Available from: https://www.nice.org.uk/guidance/ph38/chapter/Recommendations#dietary-advice

NICE (2019a) Diabetes. Available from: https://bit.ly/2PB1Ffn

NICE (2019b) Type 2 diabetes in adults: management [NG28]. Available from: https://www.nice.org.uk/Guidance/NG28

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.

Parker B, Noakes M, Luscombe N & Clifton P (2002) Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. Diabetes Care. 25(3):425-430.

PHE (2019) Public Health Outcomes Framework Indicator E12c - Preventable sight loss - diabetic eye disease. Available from: https://bit.ly/2RLxMvA

Reynolds A, Mann J, Cummings J, Winter N, Mete E & Te Morenga L (2019) Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet. 393(10170):434-445.

Rubin JK, Hinrichs-Krapels S, Hesketh R, Martin A, Herman WH & Rubino F (2016) Identifying Barriers to Appropriate Use of Metabolic/Bariatric Surgery for Type 2 Diabetes Treatment: Policy Lab Results. Diabetes Care. 39(6):954-963.

SACN (2012) SACN framework for the evaluation of evidence. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/480493/SACN_Framework_for_the_Evaluation_of_Evidence.pdf

SACN (2015) Carbohydrates and health. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf

SACN (2019) Saturated fats and health. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/814995/SACN_report_on_saturated_fat_and_health.pdf

Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S & Gibson AA (2018) Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 139:239-252.

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.

Sato J, Kanazawa A, Makita S, Hatae C, Komiya K, Shimizu T, et al (2017) A randomized controlled trial of 130 g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. Clin Nutr. 36(4):992-1000.

Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C & Boeing H (2018) A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. Eur J Epidemiol. 33(2):157-170.

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 358:j4008.

Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C & Williams SL (2018) Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Nutrition therapy. Can J Diabetes. 42:S64-S79.

SIGN (2017) Management of diabetes [116]. Available from: https://www.sign.ac.uk/assets/sign116.pdf

SIGN (2019) Management of diabetes. Available from: https://www.sign.ac.uk/sign-116-and-154-diabetes.html

Sjostrom L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, et al (2014) Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. Jama. 311(22):2297-2304.

Snorgaard O, Poulsen GM, Andersen HK & Astrup A (2017) Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Res Care. 5(1):e000354.

SSNAP (2019) Sentinel Stroke National Audit Programme National Results - Clinical. King's College London. Available from: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx

Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al (2004) The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med. 140(10):778-785.

Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, Aribisala B, Caslake M, et al (2016) Very Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiological Changes in Responders and Nonresponders. Diabetes Care. 39(5):808-815.

Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al (2014) A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes Care. 37(11):2909-2918.

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.

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. 20(4):858-871.

Unwin D & Tobin S (2015) A patient request for some "deprescribing". Bmj. 351:h4023.

USDOH & USDA (2015) Dietary Guidelines for Americans 2015-2020. 8th ed: Office of Disease Prevention and Health Promotion. Available from: https://health.gov/dietaryguidelines/2015/guidelines/

van Zuuren EJ, Fedorowicz Z, Kuijpers T & Pijl H (2018) Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. Am J Clin Nutr. 108(2):300-331.

Venn BJ & Green TJ (2007) Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationship. Eur J Clin Nutr. 61:121-122.

WHO (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Available from: https://bit.ly/2QTlcbg

WHO (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Available from: https://www.who.int/diabetes/publications/report-hba1c_2011.pdf?ua=1

Winkley K, Thomas SM, Sivaprasad S, Chamley M, Stahl D, Ismail K, et al (2013) The clinical characteristics at diagnosis of type 2 diabetes in a multi-ethnic population: the South London Diabetes cohort (SOUL-D). Diabetologia. 56(6):1272-1281.

Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, et al (2008) The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr. 87(1):114-125.

Yamada Y, Uchida J, Izumi H, Tsukamoto Y, Inoue G, Watanabe Y, et al (2014) A Non-calorie-restricted Low-carbohydrate Diet is Effective as an Alternative Therapy for Patients with Type 2 Diabetes. Internal Medicine. 53(1):13-19.